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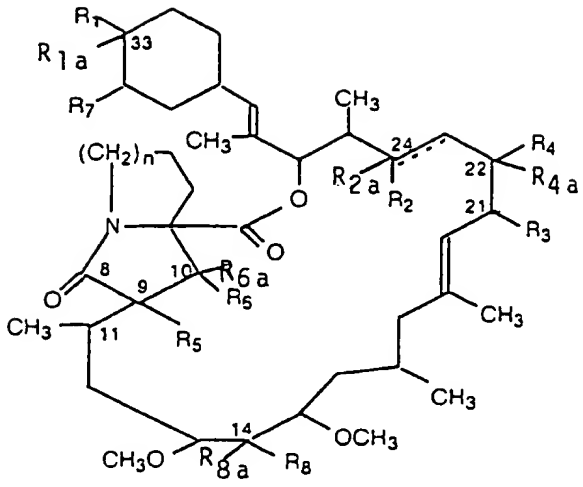
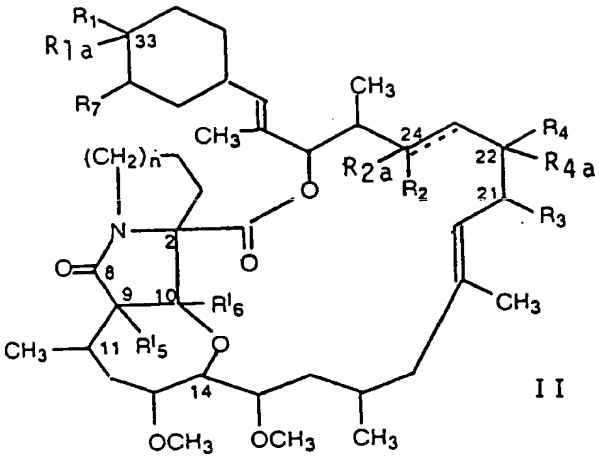
(54) Heteroatoms-containing tricyclic compounds.

(57) The invention concerns the compounds of formulae

EP 0 569 337 A1

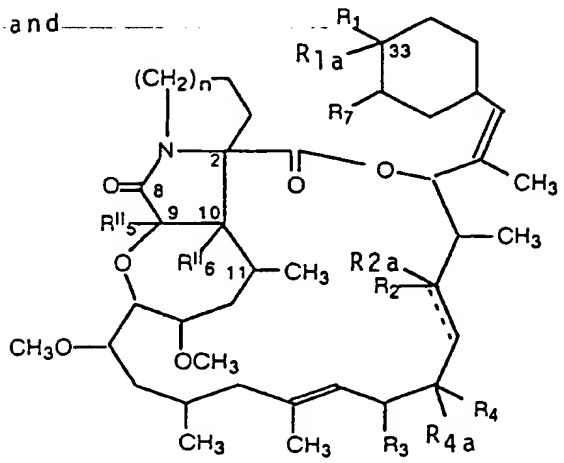


I



II

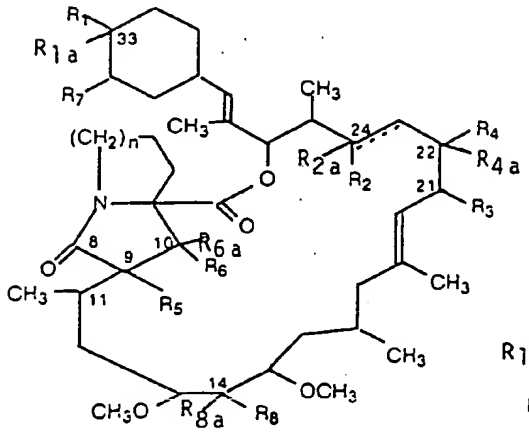
and



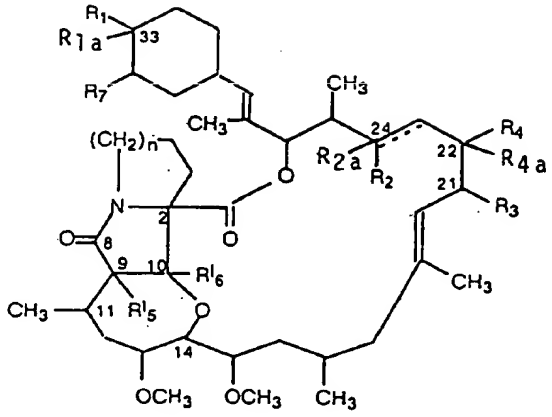
III

wherein the substituents have various significances. They can be prepared by various methods, e.g. acylation, reduction, alkylation, etc. They are indicated for use as pharmaceuticals, in particular as immunosuppressant, antiproliferative and antiinflammatory agents.

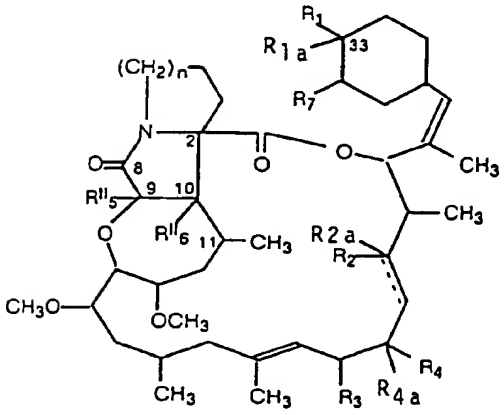
The invention relates to the field of macrolides. It concerns the compounds of formulae I to III



I



II



III

wherein

the symbol ⎯ ⎯ ⎯ represents a single bond or, when R_{2a} is absent, a double bond;

R_1 represents an optionally protected hydroxy group and R_{1a} represents hydrogen; or R_1 and R_{1a} together represent oxo;

R_2 represents an optionally protected hydroxy group or together with R_4 forms the -OC(=O)O- group, and R_{2a} represents hydrogen or is absent;

whereby when the symbol ⎯ ⎯ ⎯ is a single bond, R_2 together with R_{2a} also represents oxo;

R_3 represents methyl, ethyl, n-propyl or allyl;

R_4 represents optionally protected hydroxy or together with R_2 forms the -OC(=O)O- group, and R_{4a}

represents hydrogen;
r R_4 together with R_{4a} represents ox ;

R_5 represents alkoxycarbonyloxy, halogen, optionally protected hydroxy, lower alkoxy, acyloxy or a group $-OC(=X)N(R_{10})R_{11}$;
or R_5 together with R_{6a} forms a group $-OC(=X)N(R'_{10})-$ attached with the nitrogen atom to the carbon atom carrying R_{6a}, whereby X represents oxygen or sulfur, R_{10} and R_{11} independently represent hydrogen or lower alkyl or together with the nitrogen atom form a five- or six-membered ring optionally containing a second heteroatom such as nitrogen or oxygen, and R'_{10} is hydrogen or lower alkyl;
or R_5 together with R_{6a} represents oxy, whereby R_6 represents hydroxy;

R_6 represents hydroxy, and R_{6a} represents hydrogen or together with R_5 forms a group $-OC(=X)N(R'_{10})-$ as defined above;
or R_6 and R_{6a} together represent oxo;

R'_5 represents optionally protected hydroxy, lower alkoxy or acyloxy and R'_6 represents hydroxy;
or R'_5 and R'_6 together form the $-OC(=O)O-$ group;

R''_5 represents hydroxy or lower alkoxy and R''_6 represents hydroxy;
or R''_5 and R''_6 together form the $-OC(=O)O-$ group;

R_7 represents methoxy or hydroxy;

R_8 represents an optionally protected hydroxy group, acyloxy, imidazolylcarbonyloxy or alkoxycarbonyloxy and R_{8a} represents hydrogen;
or R_8 represents hydroxy and R_{8a} together with R_5 represents oxy;
or R_8 together with R_{8a} represents oxo; and

n represents 1 or 2;

in free form or salt form,

hereinafter briefly named "**the compounds of the invention**".

R_1 and R_2 preferably are optionally protected hydroxy. R_3 preferably is ethyl or allyl, especially ethyl. R_4 preferably is together with R_{4a} oxo. R_5 preferably is hydroxy or together with R_{8a} represents oxy. R'_5 and R''_5 preferably are hydroxy. R_8 preferably is hydroxy or oxo. R_6 preferably is together with R_{6a} oxo. R_7 preferably is methoxy. The symbol $\overline{---}$ preferably represents a single bond. n preferably is 2. X preferably is oxygen. R_{10} and R_{11} preferably are hydrogen or methyl or together with the nitrogen atom 1-imidazolyl, they especially are methyl. R'_{10} preferably is hydrogen or methyl.

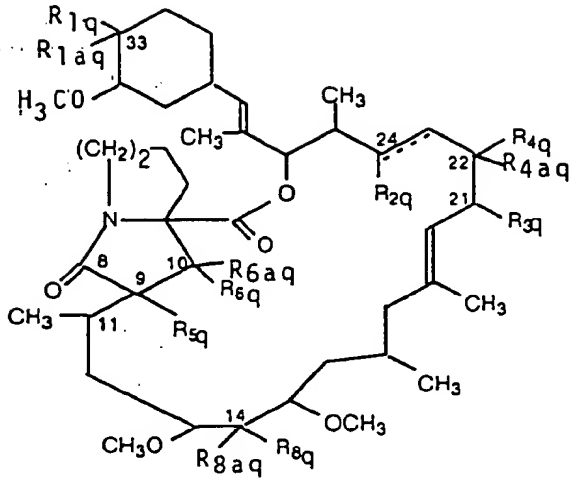
Acyl and acyloxy preferably are alkylcarbonyl or, respectively, alkylcarbonyloxy of altogether 2 to 5 carbon atoms, preferably acetyl(oxy), or formyl(oxy) or benzoyl(oxy). Halogen preferably is chlorine or bromine, it especially is chlorine. Lower alkyl and lower alkoxy preferably are of 1 to 4 carbon atoms, they especially are methyl and, respectively, methoxy. Protected hydroxy preferably is hydroxy protected by a conventional hydroxy-protecting group, it preferably is hydroxy protected by tert-butoxycarbonyl or trialkylsilyl, especially tert-butyldimethylsilyl. Alkoxycarbonyloxy preferably is of altogether 2 to 5 carbon atoms, it especially is methoxycarbonyloxy.

A compound of the invention in free form may be converted into a salt form where such forms exist, e.g. an acid addition salt form, in conventional manner and vice-versa.

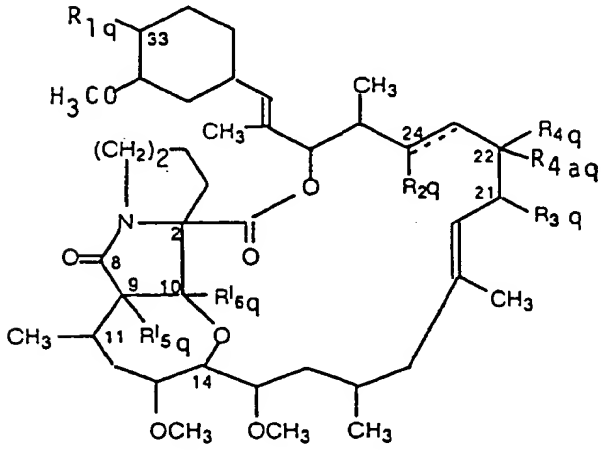
A subgroup of compounds of the invention (**compounds Ip$_1$**) is the compounds of formulae I to III as defined above, with the proviso that R_2 and R_4 are other than together the $-OC(=O)O-$ group;
R_4 is other than protected hydroxy;
R_5 is other than alkoxycarbonyloxy, halogen, protected hydroxy, a group $-OC(=X)N(R_{10})R_{11}$ as defined above or together with R_{6a} a group $-OC(=X)N(R'_{10})-$ as defined above;
R'_5 is other than protected hydroxy; and
R_8 is other than protected hydroxy or alkoxycarbonyloxy of altogether more than 2 carbon atoms.

A further subgroup of compounds of the invention (**compounds Ip$_2$**) is the compounds of formulae I to III as defined above, with the proviso that R_4, R_5 and R'_5 are other than protected hydroxy, and R_8 is other than alkoxycarbonyloxy of altogether more than 2 carbon atoms.

A further group of compounds of the invention is the **compounds of formulae Iq to IIIq**

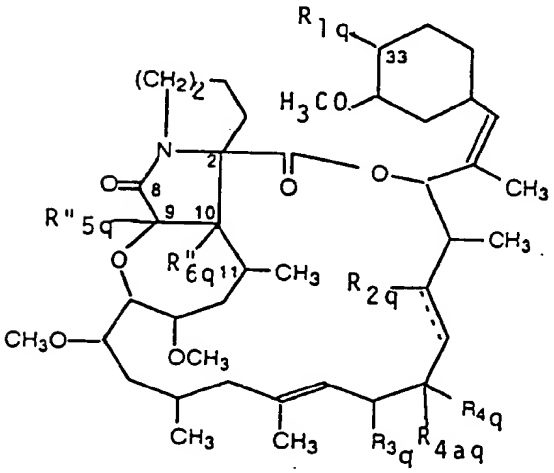


Iq



IIq

and



IIIq

wherein

R_{1q} represents hydroxy optionally protected by tert-butyldimethylsilyl or methylsulfonyl and $R1_{aq}$ represents hydrogen;
or R_{1q} and R_{1aq} together represent oxo;

R_{2q} represents hydroxy optionally protected by tert-butyldimethylsilyl or together with R_{4q} forms the -OC(=O)O- group;

R_{3q} represents ethyl or allyl;

R_{4q} represents hydroxy optionally protected by tert-butyldimethylsilyl or together with R_{2q} forms the -OC(=O)O- group, and
R_{4aq} represents hydrogen;
or R_{4q} together with R_{4aq} represents oxo;

R_{5q} represents methoxycarbonyloxy; chlorine; hydroxy optionally protected by tert-butyldimethylsilyl, tert-butoxycarbonyl or methylsulfonyl; methoxy; formyloxy, acetoxy or benzoyloxy; or a group $-OC(=O)N(R_{10q})R_{11q}$ wherein R_{10q} and R_{11q} independently represent hydrogen or methyl or together with the nitrogen atom form 4-morpholinyl;
or R_{5q} together with R_{6aq} forms a group $-OC(=X)N(R'_{10q})-$ wherein X is as defined above and R'_{10q} is hydrogen or methyl;
or R_{5q} together with R_{8aq} represents oxy, whereby R_{8q} represents hydroxy;

R_{6q} represents hydroxy, and R_{6aq} represents hydrogen or together with R_{5q} forms a group $-OC(=X)N(R'_{10q})-$ as defined above;
or R_{6q} and R_{6aq} together represent oxo;

R'_{5q} represents hydroxy optionally protected by benzoyl or acetyl and R'_{6q} represents hydroxy;
or R'_{5q} and R'_{6q} together form the -OC(=O)O- group;

R''_{5q} represents hydroxy or methoxy and R''_{6q} represents hydroxy; or R''_{5q} and R''_{6q} together form the -OC(=O)O- group; and

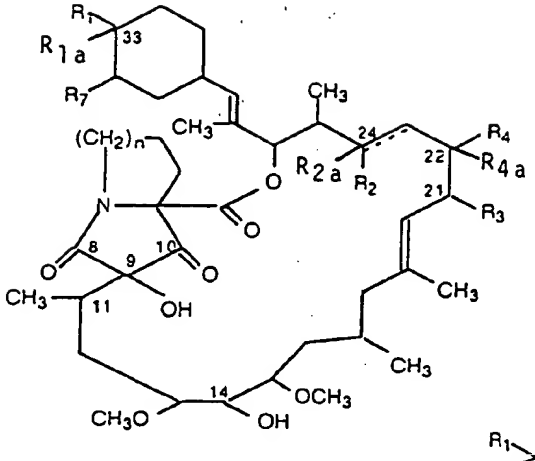
R_{8q} represents hydroxy optionally protected by tert-butyldimethylsilyl or methylsulfonyl; acetoxy or benzoyloxy; or 1-imidazolylcarbonyloxy; and
R_{8aq} represents hydrogen;
or R_{8q} represents hydroxy and R_{8aq} together with R_{5q} represents oxy;
or R_{8q} together with R_{8aq} represent oxo;

in free form or salt form.

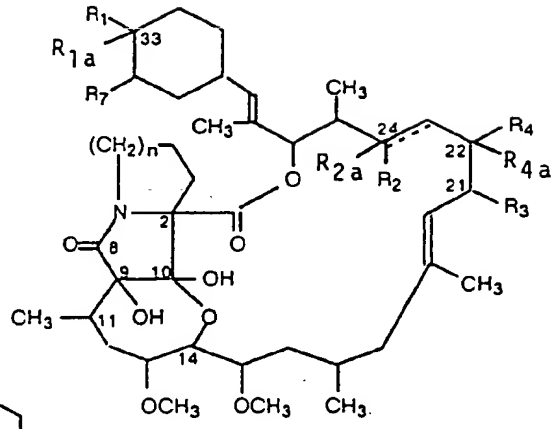
The preferred stereochemical configuration of the compounds of formulae Iq to IIIq is as indicated below for formulae Is to Vs.

The invention also provides a process for the preparation of the compounds of formulae I to III, which comprises

a) for the production of compounds of formulae

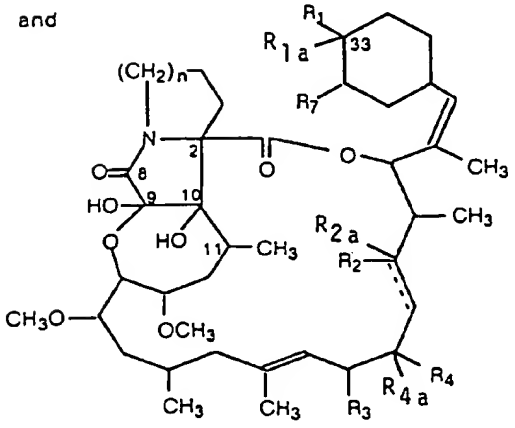


Ia



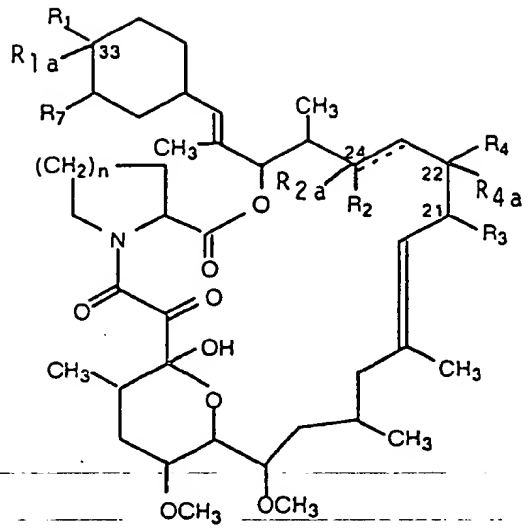
IIa

and



IIIa

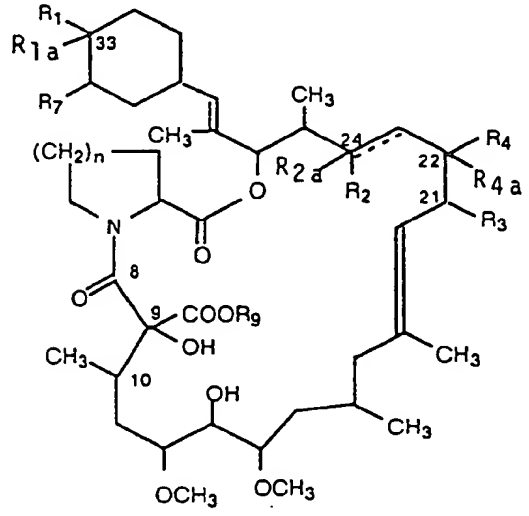
wherein the substituents are as defined above, reacting a compound of formula IV



IV

wherein the substituents are as defined above, with an appropriate base or organic or anorganic salt, optionally in the presence of a phase transfer catalyst, or

b) for the production of compounds of formula Ia or IIa, reacting a compound of formula V



V

wherein R_9 represents alkyl and the other substituents are as defined above, with an appropriate base or organic or anorganic salt, optionally in the presence of a phase transfer catalyst, or

c) for the production of compounds of formulae I to III wherein R_2 and R_4, and/or R'_5 and R'_6 respectively R''_5 and R''_6 together form the -OC(=O)O- group, reacting a compound of formula I, II or III wherein R_2 and R_4, and/or R'_5 and R'_6 respectively R''_5 and R''_6 represent hydroxy, with phosgene, diphosgene or triphosgene in the presence of an acid binder, or

d) for the production of compounds of formulae I to III wherein at least one of the substituents R_1, R_2, R_4, R_6 or R_8 represents hydroxy, appropriately reducing a compound of formula I, II or III wherein at least one of the substituents R_1, R_2, R_4, R_6 or R_8 together with R_{1a}, R_{2a}, R_{6a} or, respectively, R_{8a} represents oxo, or

e) for the production of compounds of formulae I to III wherein R_5, R'_5 and R''_5 represent lower alkoxy, appropriately alkylating a compound of formula I, II or III wherein R_5, R'_5 and R''_5 represent hydroxy, or

f) for the production of compounds of formula I or II wherein at least one of the substituents R_5, R'_5 or R_8 represents acyloxy, alkoxycarbonyloxy or $-OC(=X)N(R_{10})R_{11}$, appropriately acylating a compound f for-

mula I or II wherein at least one of the substituents R_5, R'_5 or R_8 represents hydroxy, where indicated followed by th addition of NH_3 or of an appropriate amine, r

g) for the production of compounds of formula I wherein R_8 together with R_{8a} represents oxo, appropriately oxidizing a compound of formula I wherein R_8 represents hydroxy and R_{8a} r presents hydrogen, or

h) for the production of compounds of formula I wherein R_5 represents halogen, appropriately halogenating a compound of formula I wherein R_5 represents hydroxy,

and/or optionally deprotecting the resultant compounds of formulae I to III wherein a protected hydroxy group(s) is (are) present, and/or optionally protecting the resultant compounds of formulae I to III wherein a free hydroxy group(s) is (are) present,

and recovering the resultant compounds in free form or salt form.

The process of the invention can be carried out in conventional manner.

In process variant a) and b) the reaction preferably is effected in an inert solvent, such as an ether, e.g. tetrahydrofuran, dioxane or diethylether, an aromatic hydrocarbon, e.g. benzene or toluene, an alcohol, e.g. methanol or ethanol, dimethylsulfoxide or acetonitrile. The bases or metallic salts are preferably CsF, Cs_2CO_3. K_2CO_3, LiOH, NaOH, KOH, $Mg(OR)_2$, whereby R represents a lower alkyl group, KH, NaH, a tertiary amine, e.g. triethylamine, or an amidine, e.g. 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). As phase transfer catalyst quaternated ammonium salts or preferably crown ethers, e.g. crown [18.6], may be used. The reaction is preferably carried out at a temperature between about -30° and about 50°C, especially at about room temperature. Depending on the reaction conditions used (reactants, temperature, reaction time, etc.), specific regio- and/or diastereoisomeric forms of the compounds of formula Ia, IIa or IIIa or mixtures thereof are obtained.

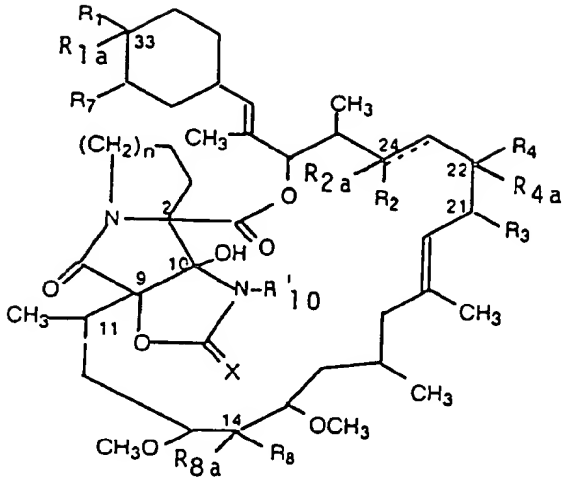
In process variant b) the configuration in position 9 is determined by the configuration at position 9 in the starting material of formula V. Reaction mixtures may be worked up in conventional manner, e.g. chromatographically.

Process variant c) for the production of the carbonates is carried out preferably in an inert solvent such as an ether, e.g. tetrahydrofuran, diethylether or dioxane, a chlorinated hydrocarbon, e.g. 1,2-dichloroethane or methylene chloride, or acetonintrile, at temperatures between about -20°C and the boiling temperature of the reaction mixture, preferably at about room temperature. A tertiary amine can be used as acid binder, e.g. triethylamine, 4-dimethylaminopyridine or pyridine.

The reduction, process variant d), can be effected in conventional manner. The reducing agent conveniently is a hydride-reagent, e.g. NaBH4, diisobutyl aluminiumhydride or tetramethylammonium triacetoxy borohydride. The process may be carried out in an inert solvent such as an ether or cyclic ether, e.g. tetrahydrofuran, dioxane or diethylether, an aromatic hydrocarbon, e.g. toluene, or in the case of tetramethylammonium triacetoxy borohydride as reducing agent, also in acetonitrile and/or acetic acid, at temperatures preferably between about -70° and about 50°C, especially at about room temperature.

Process variant e) is an alkylation. It preferably is carried out in a non-protic solvent, e.g. in an ether, a cyclic ether, an aromatic hydrocarbon, dimethyl formamide or dimethyl sulfoxide, in the presence of a base such as a non-nucleophilic nitrogen base, e.g. DBU, or an alkali hydride, e.g. sodium or potassium hydride, or a metallic salt, e.g. a carbonate or fluoride of potassium, sodium or cesium, optionally in the presence of a crown ether. The alkylating agent preferably is a halogenide, tosylate or mesylate, e.g. alkyl iodide, especially methyl iodide. The reaction is carried out at room temperature or elevated temperature, preferably at room temperature.

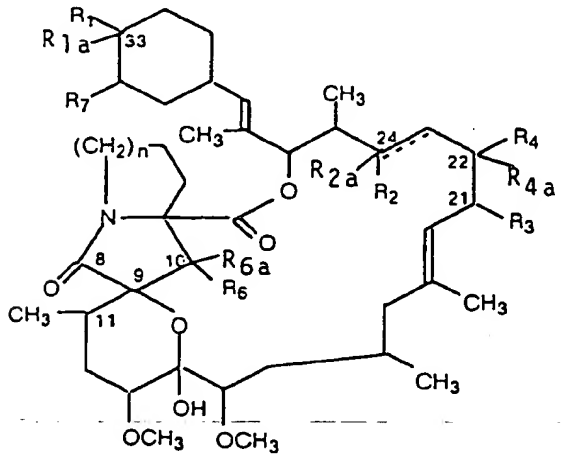
Acylation according to process variant f) can be carried out in conventional manner, e.g. in an inert solvent such as acetonitrile or dichloromethane, e.g. with an acid chloride or an acid anhydride in the presence of an acid binder such as 4-dimethylaminopyridine or with an acid in the presence of an acid binder such as 4-dimethylaminopyridine or with an acid in the presence of a carbodiimide such as dicyclohexylcarbodiimide. The acylation may be carried out with diphosgene or thiophosgene followed by the addition of NH_3 or of an appropriate amine to give the corresponding carbamates wherein R_5 represents a group of formula $-OC(=X)N(R_{10})R_{11}$ as defined above. When the reaction is carried out in the presence of NH_3 or a primary amine, the end products wherein R_6 and R_{6a} together represent oxo may undergo a cyclisation and form compounds of formula



Ib

wherein the substituents are as defined above and which also form part of the invention.

Process variant g) is an oxidation. It may be carried out in conventional manner, e.g. in an inert solvent such as an aromatic hydrocarbon, e.g toluene, or a halogenated hydrocarbon, e.g. dichloromethane or dichloroethane, at temperatures between about 0°C and room temperature, preferably at about room temperature. The reaction is effected e.g. with N-methyl-morpholine-N-oxide in the presence of a catalytic amount of tetrapropylammonium perruthenate, or with 1,1,1-tris(acetoxy)-1,1-dihydrobenziodoxol-3(1H)one (Dess-Martin method). The oxidized end compounds of formula I wherein R_8 together with R_{8a} represents oxo and R_5 represents hydroxy, may exist in equilibrium with corresponding compounds of formula I wherein R_8 represents hydroxy and R_5 together with R_{8a} represents oxy, i.e. with compounds of formula Ic



Ic

wherein the substituents are as defined above and which also form part of the invention. Process variant g) gives mixtures of these compounds which may be separated in conventional manner, e.g. chromatographically. Depending on the starting material and the reaction conditions employed, especially on the oxydizing reagent, the oxydation may take place in the positions 10, 14, 22, 24 and/or 33. Different reaction ability and/or selective protection of hydroxy groups may yield final products which are oxydized only in selected positions.

Process variant h) may be carried out in for halogenation conventional manner, e.g. by reacting with a halogenating agent such as thionyl chloride in an appropriate solvent, e.g. in pyridine or tetrahydrofuran, at temperatures e.g. between about 0°C and room temperature, preferably at about room temperature.

The process variants of the invention may be carried out simultaneously, especially process variant) may be effected in a "one pot reaction" with process variants a) or b). Mixtures of end products may be separated

in conventional manner, e.g. chromatographically.

Compounds of formula Ia may be in equilibrium with compounds of formula IIa. In many cases thes tautomeric forms may be isolated.

Process variants a) and b) signify generally

a) when reacting a compound of formula IV to obtain compounds of formulae Ia and IIa: rearrangement and cyclisation;

b) when reacting a compound of formula IV to obtain compounds of formula IIIa: cyclisation;

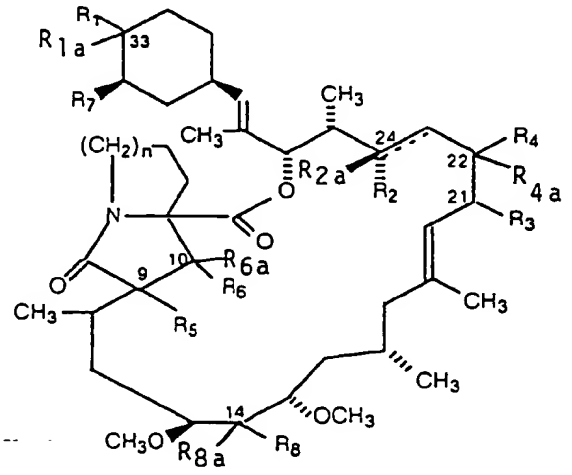
c) when reacting a compound of formula V to obtain compounds of formulae Ia and IIa: cyclisation.

When compounds obtained according to process variants a) to h) have one or more protected hydroxy group(s), the protecting group(s) may be removed in conventional manner to give the corresponding unprotected compounds. The removal of e.g. tert-butyldimethylsilyl or tert-butoxycarbonyl may be effected by treatment with hydrofluoric acid in a solvent such as acetonitrile. Depending on the reaction conditions chosen (e.g. duration or temperature) the removal can be steered in such a manner that either all or only some protecting groups are eliminated.

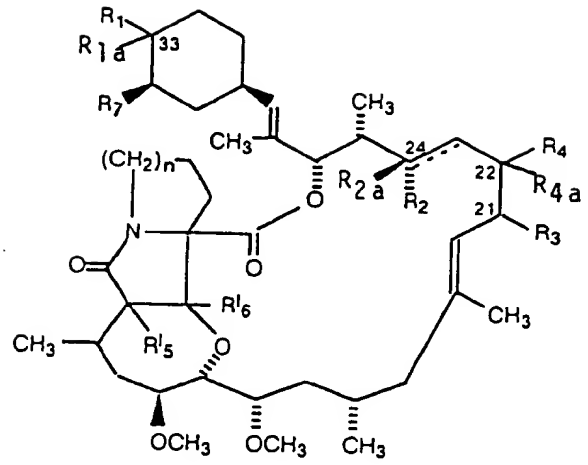
When compounds obtained according to process variants a) to h) have one or more free hydroxy group(s), the hydroxy group(s) may be protected in conventional manner to give the corresponding protected compounds. Depending on the reaction conditions chosen the reaction can be steered in such a manner that either all or only some hydroxy groups are protected. Suitable protecting groups are conventional hydroxy protecting groups such as tert-butoxycarbonyl or trialkylsilyl, preferably tert-butyldimethylsilyl.

Partial deprotection or protection is particularly indicated where a definite hydroxy group is to be reacted in a subsequent reaction step.

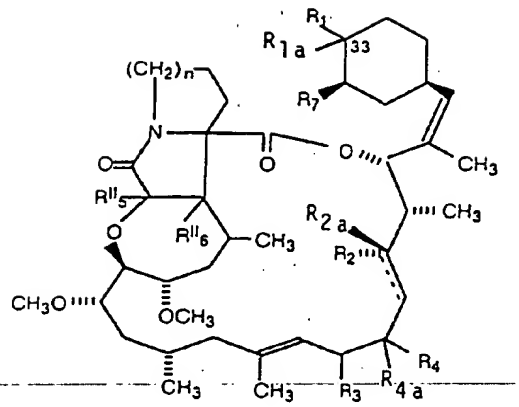
The compounds of formulae I to V have a number of chiral centers and may exist in a variety of stereoisomers. The process variants of the invention result normally in a mixture of such isomers. Depending on the conditions and the type of reaction the process can be steered in such manner that a specific isomer preferably is produced. The invention provides all optical and geometric isomers as well as racemic mixtures. The isomers may be resolved or separated by conventional techniques. However the preferred stereochemistry at various chiral carbon atoms is shown in Formulae Is to Vs:



Is



IIs



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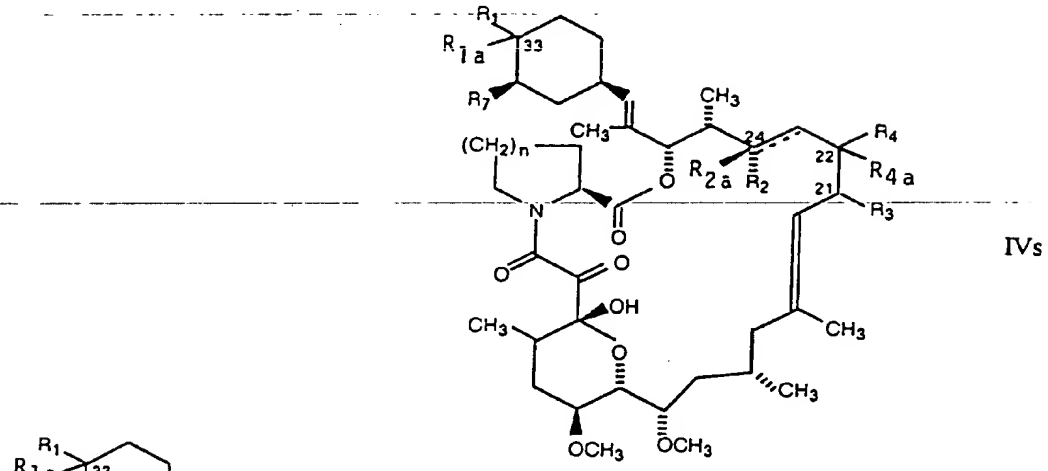
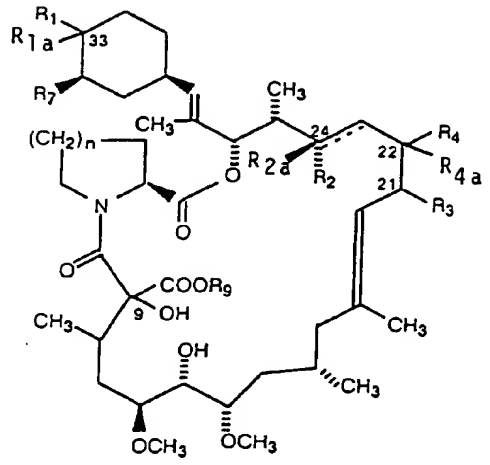


IVs



Vs

In the above formulae Is to Vs

- when R_1 is other than oxo together with R_{1a}, then R_1 preferably is bound with the α-configuration to the carbon atom in 33 position;

- R_3 preferably is bound with the (α-configuration to the carbon atom in 21 position;
- wh n R_4 is other than oxo together with R_{4a}, then R_4 preferably is bound with th α-configurati n to the carbon atom in 22 position;

A compound of the invention may be isolated and purified from the reaction mixture in conventional manner.

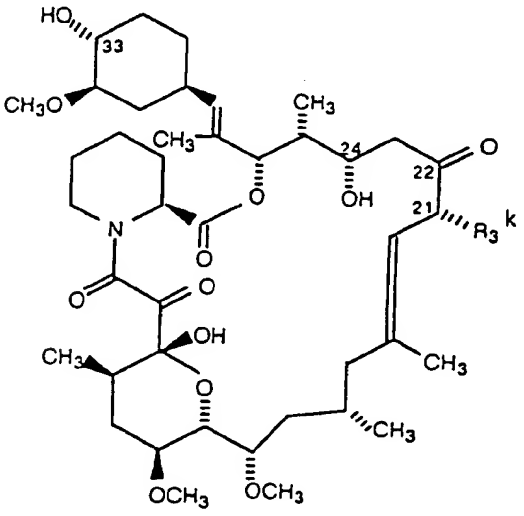
The starting material of formula V, preferably in form of the diastereoisomers hereinafter d signated diastereoisomers C, may be obtained by reacting a compound of formula IV analogously to process variant a) followed by reaction of the resultant product with a diazoalkane. The first step of this process may be carried out as described above, e.g. with KOH/crown ether in tetrahydrofuran. The reaction product is worked up in conventional manner, the residue redissolved in an inert solvent, e.g. dichloromethane, and triturated with a solution of a diazoalkane, preferably diazomethane or diazoethane, in an inert solvent, e.g. ether. The resultant reaction mixture may be worked up in conventional manner.

The starting material of formula V, preferably in form of the diastereoisomers hereinafter designated diastereoisomers A, may be obtained by reacting a compound of formula IV with a base, followed by reaction of the resultant product with a diazoalkane. This process step may be carried out in conventional manner. It preferably is effected in a mixture of solvents, e.g. in a mixture of tetrahydrofuran and water, using LiOH or $Ca(OH)_2$ as base. The reaction product is worked up in conventional manner, the residue redissolved in an inert solvent, e.g. dichloromethane, and titurated with a solution of a diazoalkane, preferably diazomethane or diazoethane, in an inert solvent, e.g. ether. The resultant reaction mixture may be worked up in conventional manner.

Insofar as their preparation is not specifically described herein, e.g. in the Examples, the compounds used as starting materials are known or can be obtained in conventional manner from known compounds, e.g. starting from appropriate Streptomyces strains such as Streptomyces tsukubaensis No. 9993 described in e.g. Fujisawa EP 184162. Samples can be obtained from the Fermentation Research Institute, Tsukuba, Ibaraki 305, Japan under provisions of the Budapest Treaty under deposit No. FERM BP-927. This strain has been redeposited on April 27, 1989 with the Agricultural Research Culture Collection International Depository, Peoria, Illinois 61604, USA under the provisions of the Budapest Treaty under deposit No. NRRL 18488.

The following Examples illustrate the invention. They are not limitative. All temperatures are in degrees Centigrade. In the NMR spectra all chemical shift values are in ppm; samples are measured in $CDCl_3$ unless indicated otherwise. The following abbreviations are used:

O-tBDMS	= tert-butyldimethylsilyloxy
db	= double bond
sb	= single bond
Im	= 1-imidazolylcarbonyl
Bz	= benzoyl
DBU	= 1,8-diazabicyclo[5.4.0]undec-7-ene
Ac	= acetyl
BOC	= tert-butoxycarbonyl



Ik

Formula Ik (R_3^k = allyl) = FK 506;
Formula Ik (R_3^k = ethyl) = FR 520.

Exampl 1: $R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; R_4 = O; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a} = R_{4a}$ = H (process a)

1a : compound of formula IIIa
1b: compound of formula IIa (diastereoisomer A)
1c: compound of formula Ia (diastereoisomer A)
1d: compound of formula Ia (diastereoisomer B)
1e: compound of formula Ia (diastereoisomer C)

4 g of crown[18.6]ether and 12.7 g of cesium carbonate (or 5 g of cesium fluoride) are added to a solution of 20 g 24,33-bis-O-tBDMS-FR 520 in 250 ml of dry tetrahydrofuran. The reaction mixture is stirred for 3 hours at room temperature, then partitioned between ethyl acetate and 1 N hydrochloric acid, the phases are separated, the organic phase is washed with brine, dried over sodium sulfate, filtered and evaporated under vacuum. Chromatography of the residue (n-hexane/ethyl acetate = 3/1 → 1/2) gives the title substances as colourless foams.

Example 2: $R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a}$ = O; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a}$ = H; diastereoisomers A (process b)

2a : compound of formula IIa
2b: compound of formula Ia

1 ml of diazabicycloundecene is added to a solution of 5.2 g of the compound of formula V ($R_1 = R_2$ = O-tBDMS; $R_{1a} = R_{2a}$ = H; $R_3 = C_2H_5$; $R_4 + R_{4a}$ = O; $R_7 = OCH_3$; $R_9 = CH_3$; n = 2; ⎓ = sb; diastereoisomer A) in 250 ml of acetonitrile. The reaction mixture is stirred for 70 minutes at room temperature and then worked up as described in example 1 (n-hexane/ethyl acetate = 3/2) to give the title substances as colourless foams.

Analogously as described in examples 1 and 2 the following compounds of formulae Ia, IIa and IIIa are obtained in form of colourless foams ($R_7 = OCH_3$; n = 2; ⎓ = sb; $R_{1a} = R_{2a}$ = H):

ex:	form.	isomer	R_1	R_2	R_4	R_{4a}	R_3	starting material:
3a	IIIa	-	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	24,33-di-O-tBDMS-FK 506
3b	IIa	A	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	
3c	Ia	A	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	
3d	Ia	C	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	
4	IIIa	-	$-O-SO_2-CH_3$	-O-tBDMS	O		$-C_2H_5$	Compound A)
5	IIIa	-	$-O-SO_2-CH_3$	-O-tBDMS	O		$-CH_2CH=CH_2$	Compound B)
6a	IIIa	-	-OH	-OH	O		$-C_2H_5$	FR 520
6b	IIa	A	-OH	-OH	O		$-C_2H_5$	
6c	Ia	A	-OH	-OH	O		$-C_2H_5$	
6d	Ia	B	-OH	-OH	O		$-C_2H_5$	
6e	Ia	C	-OH	-OH	O		$-C_2H_5$	
6f	Ia	D	-OH	-OH	O		$-C_2H_5$	
7a	IIIa	-	-OH	-OH	O		$-CH_2CH=CH_2$	FK 506
7b	IIa	A	-OH	-OH	O		$-CH_2CH=CH_2$	
7c	Ia	A	-OH	-OH	O		$-CH_2CH=CH_2$	
7d	Ia	B	-OH	-OH	O		$-CH_2CH=CH_2$	
7e	Ia	C	-OH	-OH	O		$-CH_2CH=CH_2$	
8	Ia	A	-O-tBDMS	-OH	O		$-C_2H_5$	33-O-tBDMS-FR520 a)
9a	IIIa	-	-O-tBDMS	-O-CO-O-		H	$-C_2H_5$	Compound G)
9b	Ia	A	-O-tBDMS	-O-CO-O-		H	$-C_2H_5$	
9c	Ia	C	-O-tBDMS	-O-CO-O-		H	$-C_2H_5$	
10	Ia	C	-O-tBDMS	-O-tBDMS	O		$-C_2H_5$	Compound C)
11	Ia	C	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	Compound D)
12a	Ia	A	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	Compound F)
12b	IIa	A	-O-tBDMS	-O-tBDMS	O		$-CH_2CH=CH_2$	

a) Deprotection or, respectively, reduction of this compound gives the compound of Example 6c (= Example 73) or, respectively, of Example 28

Example 13: Compound of formula III ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a}$ = O; $R''_5 + R''_6$ = OCO-O; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a}$ = H (process c)

To a solution of 0.8 g of the compound of formula III ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a}$ = O; $R''_5 = R''_6$ = OH; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a}$ = H) in 40 ml of acetonitrile are added in turn 0.2 ml of diphosgene and 1.75 g of dimethylaminopyridine. The reaction mixture is stirred for 1.5 hours at room temperature and then worked up as described in example 1 (n-hexane/ethyl acetate = 9/1) to give the title substance in form of a colourless foam.

Analogously as described in example 13 the following compounds of formulae I to III are obtained in form of colourless foams ($R_3 = C_2H_5$; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a} = R_{4a} = R_{8a}$ = H):

ex:	form.	isomer	R_1	R_2	R_4	R_5 / R'_5 / R''_5	R_6 / R'_6 / R''_6	R_8	starting material:
14	II	A	-O-tBDMS	-O-tBDMS	-O-tBDMS	-O-CO-O-		-	Ex. 1b
15	I	A	-O-tBDMS	-O-CO-O-		OH	O*	OH	Ex. 28
16	I	C	-OH	-O-CO-O-		-O-BOC	O*	OH	Ex. 27
17	III	-	-OH	-O-CO-O-		-O-CO-O-		-	Ex. 25
18	I	B	-OH	-O-CO-O-		OH	O*	OH	Ex. 26a

* together with R_{6a}

Example 19: Compound of formula I (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R_5 = R_6 = R_8 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = R_{6a} = R_{8a} = H; diastereoisomer C) (process d)

0.5 g of tetramethylammonium triacetoxy boronhydride are added to a solution of 1 g of the compound of formula I (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_{1a} = R_{2a} = R_{8a} = H; R_4 + R_{4a} = R_6 + R_{8a} = O; R_5 = R_8 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; diastereoisomer C) in 30 ml of acetonitrile and 5 ml of acetic acid. The reaction mixture is stirred for 3.5 hours at room temperature and then partitioned between saturated aqueous $NaHCO_3$-solution and ethyl acetate. The organic phase is separted, washed in turn with brine, 1 N hydrochloric acid and brine again, dried over Na_2SO_4, filtered and evaporated under vacuum. Chromatography of the residue (ethyl acetate) gives the title substance in form of a colourless foam.

Analogously as described in example 19 the following compounds of formulae I, II and III are obtained in form of colourless foams (R_3 = C_2H_5; R_7 = OCH_3; R_8 = OH; R_{1a} = R_{2a} = H; ⎓ = sb; n = 2):

ex:	form.	isomer	R_1	R_2	R_4	R_{4a}	R_5 R'_5 R''_5	R_6 R'_6 R''_6	R_{6a}	starting material
20	I	B	-O-tBDMS	-O-tBDMS	O		OH	OH	H	Ex. 1d
21	I	A	-O-tBDMS	-O-tBDMS	O		OH	OH	H	Ex. 1c
22	II	A	-O-tBDMS	-O-tBDMS	OH	H	OH	OH	-	Ex. 1b
23a	I	A/cis	OH	-O-CO-O-		H	OH	OH	H	Ex. 112
23b	I	A/trans	OH	-O-CO-O-		H	OH	OH	H	Ex. 112
24a	I	C	-O-tBDMS	-O-tBDMS	OH	H	OH	O		Ex. 1e a)
24b	I	C	-O-tBDMS	-O-tBDMS	OH	H	OH	OH	H	Ex. 1e a)
25	III	-	-O-tBDMS	-O-tBDMS	OH	H	-O-CO-O-		-	Ex. 100
26a	I	B	OH	OH	OH	H	OH	O		Ex. 6d
26b	I	B	OH	OH	OH	H	OH	OH	H	Ex. 6d
27	I	C	OH	OH	OH	H	O-BOC	O		Ex. 115
28	I	A	-O-tBDMS	OH	OH	H	OH	O		Ex. 8

a) Deprotection gives the compound of Example 118

Example 29: Compound f formula I ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a}$ = O; $R_5 = R_7 = OCH_3$; R_8 = OH; ⎓ = sb; n = 2; $R_{1a} = R_{2a} = R_{8a}$ = H) (process d)

200 mg of crown[18.6]ether, 200 mg of cesium carbonate and 1.5 ml of methyl iodide ar added to a solution of 100 mg of the compound of formula I ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_{1a} = R_{2a} = R_{8a}$ = H; $R_4 + R_{4a} = R_6 + R_{6a}$ = O; $R_5 = R_8$ = OH; $R_7 = OCH_3$; ⎓ = sb; n = 2; diastereoisomer A) and stirred for 1.5 hours at room temperature. The reaction mixture is worked up as described in example 1 (n-hexane/ethyl acetate = 2/1) to give the title substance in form of a colourless foam.

Analogously as described in example 29 the following compounds of formula I and III are obtained in form of colourless foams ($R_3 = C_2H_5$; $R_{1a} = R_{2a} = R_{8a}$ = H; $R_4 + R_{4a}$ = O; $R_7 = OCH_3$; R_8 = OH; ⎓ = sb; n = 2):

ex:	form.	isomer	R_1	R_2	R_5	R''_6 R_6	R_{6a}	starting material
30	III	-	-O-tBDMS	-O-tBDMS	$-OCH_3$	OH	-	Ex. 1a
31	I	C	-O-tBDMS	-O-tBDMS	$-OCH_3$	O		Ex. 1e

Example 32: $R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a}$ = O; $R_7 = OCH_3$; ⎓ = sb; n = 2; $R_{1a} = R_{2a}$ = H; diastereoisomer A (process f)

32a: compound of formula I (R_5 = OH; $R_6 + R_{6a}$ = O; R_8 = O-Bz; R_{8a} = H)
32b: compound of formula I (R_5 = O-Bz; $R_6 + R_{6a}$ = O; R_8 = O-Bz; R_{8a} = H)
32c: compound of formula I (R_5 = O-Bz; $R_6 + R_{6a}$ = O; R_8 = OH; R_{8a} = H)
32d: compound of formula II (R'_5 = O-Bz; R'_6 = OH)

5 mol equivalents of 4-dimethylaminopyridine and 1.3 mol equivalents of benzoyl chloride are added to a solution of 0.6 g of the compound of formula I ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_{1a} = R_{2a} = R_{8a}$ = H; $R_4 + R_{4a} = R_6 + R_{6a}$ = O; $R_5 = R_8$ = OH; $R_7 = OCH_3$; ⎓ = sb; n = 2; diastereoisomer A) or of the compound of formula II ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_{1a} = R_{2a}$ = H; $R_4 + R_{4a}$ = O; R'_5 = OH; R'_6 = OH; $R_7 = OCH_3$; ⎓ = sb; n = 2). The reaction mixture is stirred for 45 minutes and then worked up as described in example 1 (n-hexane/ethyl acetate = 4/1 → 2/1) to yield the title substances in form of colourless foams.

Analogously as described in example 32 the following compounds of formula I and II are obtained in form of colourless foams ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_{1a} = R_{2a}$ = H; $R_4 + R_{4a}$ = O; $R_7 = OCH_3$; ⎓ = sb; n = 2):

ex:	form.	isomer	R_5	R_6 R'_6	R_{6a}	R_8	R_{8a}	starting material
33	I	A	OH	O		O-Im	H	Ex. 1b or 1c
34	I	C	O-Ac	O		O-Ac	H	Ex. 1e
35a	I	C	O-Bz	O		O-Bz	H	Ex. 1e
35b	I	C	O-Bz	O		OH	H	
36a	I	C	$-O-SO_2CH_3$	O		$-O-SO_2CH_3$	H	Ex. 1e
36b	I	C	OH	O		$-O-SO_2CH_3$	H	
37a	I	A	O-Ac	O		O-Ac	H	Ex. 1b or 1c
37b	I	A	OH	O		O-Ac	H	
37c	I	A	O-Ac	O		OH	H	
37d	II	A	O-Ac	OH	-	-	-	
38	I	A	-O-CHO	O		O		Ex. 50
39	I	A	$-O-COOCH_3$	O		-OtBDMS	H	Ex. 58b
40	I	A	-O-CHO	O		-OtBDMS	H	Ex. 58b a)
41	I	B	-O-CHO	O		-OtBDMS	H	Ex. 60a
42	I	C	-O-CHO	O		-OtBDMS	H	Ex. 59
43	I	C	-O-BOC	O		-OtBDMS	H	Ex. 59

a) Deprotection gives the compound of Example 6c (= Example 73)

Example 44: Compound of formula I (R_1 = R_2 = R_8 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = R_6 + R_{6a} = O; R_5 = O-CO-(4-morpholinyl); R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = R_{8a} = H; diastereoisomer A) (process f)

10 equ. of 4-dimethylaminopyridine and 1 molequ. of diphosgene are added to a solution of 2 g of the compound of formula I (R_1 = R_2 = R_8 = O-tBDMS; R_3 = C_2H_5; R_{1a} = R_{2a} = R_{8a} = H; R_4 + R_{4a} = R_6 + R_{6a}= O; R_5 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; diastereoisomer A) in 50 ml of acetonitrile, the reaction mixture is stirred for 20 minutes at room temperature, then poured onto 500 ml of ethyl acetate and 20 ml of morpholine, rigorously stirred for 10 minutes and then worked up as described in example 1 (n-hexane/ethyl acetate = 7/1) to yield the substance as a colourless foam.

Analogously as described in example 44 the following compounds of formula I and Ib are obtained in form of colourless foams (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R_7 = OCH_3; ⎓ = sb; n = 2; R_6 = OH; R_{1a} = R_{2a} = R_{8a} = H):

ex.	form.	isomer	R_5	R_8	R_{8a}	starting material
45	I	A	$-O-CO-NH_2$	-O-tBDMS	H	Ex. 58b
46	I	A	$-O-CO-N(CH_3)_2$	-O-tBDMS	H	Ex. 58b
47a	Ib	C	-	O		(R'_{10} = H, X = O) Ex. 51
47b	I	C	$-O-CO-NH_2$	O		
48	Ib	A	-	-O-tBDMS	H	(R'_{10} =CH_3, X= O) Ex. 58b
49	Ib	A	-	-O-tBDMS	H	(R'_{10} =CH_3, X= S) Ex. 58b

Example 50: Compound of formula I (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = R_6 + R_{6a} = R_8 + R_{8a} = O; R_5 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = H; diastereoisomer A) (process g)

0.5 g of 1,1,1-tris(acetoxy)-1,1-dihydro-benziodoxol-3(1H)-one are added to a solution of 0.5 g of the compound of formula I (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = R_6 + R_{6a} = O; R_5 = R_8 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = R_{8a} = H; diastereoisomer A) in 50 ml of methylene chlorid . The reaction mixture

is stirred for 3 hours at room temperature, then filtered over silicagel, washed with n-hexane/ thyl acetate (1/1) and the filtrate evaporated und r vacuum. Chromatography of the residue (n-hexane/ethyl acetate = 3/1) giv s the title substance in form of a colourless foam.

Analogously as described in example 50 the following compounds of formula I are obtained in form of colourless foams ($R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = R_8 + R_{8a} = O$; $R_7 = OCH_3$; $\overline{---}$ = sb; n = 2; R_{2a} = H):

ex.	isomer	R_1	R_{1a}	R_2	R_5	starting material
51	C	-O-tBDMS	H	-O-tBDMS	OH	Ex. 1e
52	A	O		-O-tBDMS	OH	Ex. 70
53	A	-O-tBDMS	H	-O-tBDMS	OCH_3	Ex. 29
54	C	-O-tBDMS	H	-O-tBDMS	OCH_3	Ex. 31

Example 55: Compound of formula I ($R_1 = R_2 = R_8$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; R_8 = Cl; $R_7 = OCH_3$; $\overline{---}$ = sb; n = 2; $R_{1a} = R_{2a} = R_{8a}$ = H; diastereoisomer epi-A) (process h)

0.3 ml of thionyl chloride in 5 ml of pyridine are added to a solution of 1 g of the compound of formula I ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; R_5 = OH; $R_7 = OCH_3$; R_8 = O-tBDMS; $R_{1a} = R_{2a} = R_{8a}$ = H; $\overline{---}$ = sb; n = 2; diastereoisomer A) in 100 ml of tetrahydrofuran, the reaction mixture is stirred at room temperature for 15 hours and then partitioned between ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The organic phase is separated, washed twice with 1 N HCl and water, dried over Na_2SO_4 and the solvents are removed under vacuo. Column chromatography (n-hexane/ethyl acetate = 9/1) gives the title compound as a colourless foam.

Analogously as described in example 55 the following compounds of formula I are obtained in form of colourless foams ($R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; $R_7 = OCH_3$; R_8 = O-tBDMS; $R_{1a} = R_{2a} = R_{8a}$ = H; $\overline{---}$ = sb; n = 2):

ex:	isomer	R_1	R_2	R_5	starting material
56	epi-C	-O-tBDMS	-O-tBDMS	Cl	Ex. 59
57	epi-B	-O-tBDMS	-O-tBDMS	Cl	Ex. 60a

Example 58: Compound of formula I ($R_1 = R_2 = R_8$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; $R_7 = OCH_3$; $\overline{---}$ = sb; n = 2; $R_{1a} = R_{2a} = R_{8a}$ = H; diastereoisomer A) (protection)

a) R_5 = O-tBDMS

b) R_5 = OH

5 equ. of 2,6-lutidine and 2 equ. of t.butyldimethylsilyl triflate are added to a solution of the compound of formula I ($R_1 = R_2$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; $R_5 = R_8$ = OH; $R_7 = OCH_3$; $R_{1a} = R_{2a} = R_{8a}$ = H; $\overline{---}$ = sb; n = 2; diastereoisomer A) in 50 ml of acetonitrile, the reaction mixture is stirred for 1.5 hours at room temperature and then worked up as described in example 1. Chromatography (eluent = toluene) gives the title compounds as colourless foams.

Analogously as described in example 58 the following compounds of formula I are obtained in form of colourless foams ($R_1 = R_2 = R_8$ = O-tBDMS; $R_3 = C_2H_5$; $R_4 + R_{4a} = R_6 + R_{6a} = O$; $R_7 = OCH_3$; $\overline{---}$ = sb; n = 2; $R_{1a} = R_{2a} = R_{8a}$ = H):

ex:	isomer	R_5	starting material:
59	C	OH	Ex. 1e
60a	B	OH	} Ex. 1d
60b	B	-O-tBDMS	} Ex. 1d

Example 61: Compound of formula III (R_1 = OH; R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R''_5 = R''_6 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = H) (partial deprotection)

3 ml of 40 % aqueous hydrofluoric acid are added to a solution of 0.5 g of the compound of formula III (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R''_5 = R''_6 = OH; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = H) in 30 ml of acetonitrile. The reaction mixture is stirred for 5 minutes at room temperature, then partitioned between saturated aqueous $NaHCO_3$-solution and ethyl acetate, the organic phase is separated, washed with saturated aqueous $NaHCO_3$-solution and several times with water, dried over Na_2SO_4, filtered and evaporated under vacuum. Chromatography of the residue (n-hexane/ethyl acetate = 1/2) gives the title substance as a colourless foam.

Analogously as described in example 61 the following compounds are obtained in form of colourless foams (R_1 = OH; R_4 + R_{4a} = O; R_7 = OCH_3; ⎓ = sb; n = 2; R_{1a} = R_{2a} = H):

ex:	form.	isomer	R_2	R_3	R_5 R'_5 R''_5	R_6 R'_6 R''_6	R_{6a}	R_8	R_{8a}	start. mat.
62	III	-	-O-tBDMS	$-CH_2CH=CH_2$	OH	OH	-	-	-	Ex. 3a
63	II	A	-O-tBDMS	$-CH_2CH=CH_2$	OH	OH	-	-	-	Ex. 3b
64	I	A	-O-tBDMS	$-CH_2CH=CH_2$	OH	O		OH	H	Ex. 3c
65	III	-	-O-tBDMS	$-C_2H_5$	OCH_3	OH	-	-	-	Ex. 30
66	I	A	-O-tBDMS	$-C_2H_5$	OCH_3	O		OH	H	Ex. 29
67	I	A	-O-tBDMS	$-C_2H_5$	OH	O		O-Im	H	Ex. 33
68	I	A	-O-tBDMS	$-C_2H_5$	OH	O		O		Ex. 50
69a	I	A	-O-tBDMS	$-C_2H_5$	O-tBDMS	O		-O-tBDMS	H	Ex. 58a
69b	I	A	OH	$-C_2H_5$	O-tBDMS	O		-O-tBDMS	H	Ex. 58a
69c	I	A	OH	$-C_2H_5$	O-tBDMS	O		OH	H	Ex. 58a
69d	I	A	-O-tBDMS	$-C_2H_5$	O-tBDMS	O		OH	H	Ex. 58a
70	I	A	-O-tBDMS	$-C_2H_5$	OH	O		OH	H	Ex. 1c a)

a) Deprotection gives the compound of Example 6c (= Example 73)

Example 71: Compound of formula I (R_1 = R_2 = R_3 = R_8 = OH; R_3 = C_2H_5; R_4 + R_{4a} = R_6 + R_{6a} = O; R_7 = OCH_3; R_{1a} = R_{2a} = R_{8a} = H; ⎓ = sb ; n = 2; diastereoisomer B) (deprotection)

3 ml of 40 % aqueous hydrofluoric acid are added to a solution of 0.5 g of the compound of formula I (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = R_6 + R_{6a} = O; R_5 = R_8 = OH; R_7 = OCH_3; R_{1a} = R_{2a} = R_{8a} = H; ⎓ = sb; n = 2; diastereoisomer B) in 30 ml of acetonitrile. The reaction mixture is stirred for 4 hours at room temperature, then partitioned between saturated aqueous $NaHCO_3$-solution and ethyl acetate, the organic phase is separated, washed with saturated aqueous $NaHCO_3$ -solution and several times with water, dried over Na_2SO_4, filtered and evaporated under vacuum. Chromatography of the residue (n-hexane/ethyl acetate = 1/2) gives the title substance as a colourless foam.

Analogously as described in example 71 the following compounds are obtained in form of colourless foams ($R_7 = OCH_3$; $R_{2a} = H$; ——— = sb; n = 2):

ex:	form.	isomer	R_1	R_{1a}	R_3	R_2	R_4	R_{4a}	R_5 / R'_5 / R''_5	R_6 / R'_6 / R''_6	R_{6a}	R_8	R_{8a}	start. mat.
72	II	A	OH	H	$-C_2H_5$	OH	O		OH	OH	-	-	-	Ex. 1b
73	I	A	OH	H	$-C_2H_5$	OH	O		OH		O	OH	H	Ex. 1c,8, 48 or 70
74	III	-	OH	H	$-C_2H_5$	OH	O		OH	OH	-	-	-	Ex. 1a
75	I	C	OH	H	$-C_2H_5$	OH	O		OH		O	OH	H	Ex.1e or 115
76	III	-	OH	H	$-CH_2CH=CH_2$	OH	O		OH	OH	-	-	-	Ex.3a or 62
77	II	A	OH	H	$-CH_2CH=CH_2$	OH	O		OH	OH	-	-	-	Ex.3b or 63
78	I	A	OH	H	$-CH_2CH=CH_2$	OH	O		OH		O	OH	H	Ex.3c or 64
79	I	C	OH	H	$-CH_2CH=CH_2$	OH	O		OH		O	OH	H	Ex. 3d
80	III	-	$-O-SO_2-CH_3$	H	$-C_2H_5$	OH	O		OH	OH	-	-	-	Ex. 4
81	III	-	$-O-SO_2-CH_3$	H	$-CH_2CH=CH_2$	OH	O		OH	OH	-	-	-	Ex. 5
82	I	C	OH	H	$-C_2H_5$	OH	O		OH	OH	H	OH	H	Ex. 19
83	I	B	OH	H	$-C_2H_5$	OH	O		OH	OH	H	OH	H	Ex. 20
84	I	A	OH	H	$-C_2H_5$	OH	O		OH	OH	H	OH	H	Ex. 21
85	II	A	OH	H	$-C_2H_5$	OH	OH	H	OH	OH	-	-	-	Ex. 28
86	III	-	OH	H	$-C_2H_5$	OH	O		OCH_3	OH	-	-	-	Ex. 30
87	I	A	OH	H	$-C_2H_5$	OH	O		OCH_3		O	OH	H	Ex. 29
88	I	C	OH	H	$-C_2H_5$	OH	O		OCH_3		O	OH	H	Ex. 31
89	I	A	OH	H	$-C_2H_5$	OH	O		O-Bz		O	OH	H	Ex. 32c
90	I	A	OH	H	$-C_2H_5$	OH	O		O-Bz		O	O-Bz	H	Ex. 32b
91	I	A	OH	H	$-C_2H_5$	OH	O		OH		O	O-Im	H	Ex. 33 or 67
92	I	A	O		$-C_2H_5$	OH	O		OH		O	O		Ex. 52
93	I	A	OH	H	$-C_2H_5$	OH	O		OH		O	O		Ex. 50 a)
94	I	C	OH	H	$-C_2H_5$	OH	O		OH		O	O		Ex. 51

a) In equilibrium in solution with the hemiketal form ($R_5 + R_{8a} = -O-$; $R_8 = OH$)

ex:	form.	isomer	R_1	R_{1a}	R_3	R_2	R_4	R_{4a}	R_5 / R'_5 / R''_5	R_6 / R'_6 / R''_6	R_{6a}	R_8	R_{8a}	start. mat.
95	I	A	OH	H	$-C_2H_5$	OH	O		O-Ac	O		O-Ac	H	Ex. 37a
96	I	A	OH	H	$-C_2H_5$	OH	O		OH	O		O-Ac	H	Ex. 37b
97	I	A	OH	H	$-C_2H_5$	OH	O		O-Ac	O		OH	H	Ex. 37c
98	II	A	OH	H	$-C_2H_5$	OH	O		O-Ac	OH	-	-	-	Ex. 37d
99	I	C	OH	H	$-C_2H_5$	OH	O		O-Ac	O		O-Ac	H	Ex. 34
100	III	-	OH	H	$-C_2H_5$	OH	O		-O-CO-O-		-	-	-	Ex. 13
101	II	A	OH	H	$-C_2H_5$	OH	O		-O-CO-O-		-	-	-	Ex. 14
102	I	A	OH	H	$-C_2H_5$	OH	OH	H	OH	O		OH	H	Ex. 28
103	I	A	OH	H	$-C_2H_5$	OH	O		$-O-COOCH_3$	O		OH	H	Ex. 39
104	I	A	OH	H	$-C_2H_5$	OH	O		b)	O		OH	H	Ex. 44
105	I	A	OH	H	$-C_2H_5$	OH	O		$-O-CO-NH_2$	O		OH	H	Ex. 45
106	I	A	OH	H	$-C_2H_5$	OH	O		$-O-CO-N(CH_3)_2$	O		OH	H	Ex. 46
107	I	C	OH	H	$-C_2H_5$	OH	O		$-O-CO-NH_2$	O		O		Ex. 47b
108	I	A	OH	H	$-C_2H_5$	OH	O		Cl	O		OH	H	Ex. 55
109	I	C	OH	H	$-C_2H_5$	OH	O		Cl	O		OH	H	Ex. 56
110	I	A	OH	H	$-C_2H_5$	OH	O		$-OCH_3$	O		O		Ex. 53
111	I	C	OH	H	$-C_2H_5$	OH	O		$-OCH_3$	O		O		Ex. 54
112	I	A	OH	H	$-C_2H_5$	-O-CO-O-		H	OH	O		OH	H	Ex. 15
113	I	C	OH	H	$-C_2H_5$	-O-CO-O-		H	OH	O		OH	H	Ex. 16
114	I	C	OH	H	$-C_2H_5$	OH	OH	H	OH	OH	H	OH	H	Ex. 24b
115	I	C	OH	H	$-C_2H_5$	OH	O		-O-BOC	O		OH	H	Ex. 43 a)
116	Ib	C	OH	H	$-C_2H_5$	OH	O		-	-	-	O (R'_{10}= H; X=O)		Ex. 47a
117	III	-	OH	H	$-C_2H_5$	-O-CO-O-		H	OH	OH	-	-	-	Ex. 9a
118	I	C	OH	H	$-C_2H_5$	OH	OH	H	OH	O		OH	H	Ex. 24a

a) Deprotection gives the compound of Example 6e (= Example 75)

b) R_5 = $-O-CO-N[-(CH_2)_2O(CH_2)_2-]$ (4-morpholinylcarbonyloxy)

The starting materials may be obtained as follows:

A) 33-O-Methanesulfonyl-24-O-tBDMS-FR 520

3 g of dimethylaminopyridine and 0.3 ml of methanesulfonic acid chloride are add d to a solution of 1 g of 24-O-tBDMS-FR 520 in 40 ml of acetonitrile and stirred at room temperature for 2 hours. Then the reaction mixture is partitioned between saturated aqueous $NaHCO_3$-solution and ethyl acetate, the phases are separated, the organic phase is washed with 1 N hydrochloric acid and brine, dried over sodium sulfate, filtered and evaporated under vacuum. Chromatography of the residue (n-hexane/ethyl acetate = 1/1) yields the title compound as a colourless foam.

B) 33-O-Methanesulfonyl-24-O-tBDMS-FK 506

Using 24-O-tBDMS-FK 506 as starting material and proceeding analogously as described in A) gives the title compound as a colourless foam.

C) Compound of formula V (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R_7 = OCH_3; R_9 = CH_3; R_{1a} = R_{2a} = H; ⎯⎯ = sb; n= 2; diastereoisomer C)

0.5 g of crown[18.6]ether and 0.7 g of 24,33-bis-O-tBDMS-FR 520 are added to a suspension of 47 mg of powdered KOH in 40 ml of tetrahydrofuran. The reaction mixture is stirred for 20 minutes at room temperature, then partitioned between 1 N hydrochloric acid and ethyl acetate, the phases are separated, the organic phase is washed with brine, dried over sodium sulfate and evaporated under vacuum. The residue is redissolved in 30 ml of dichloromethane and triturated with a 1 M solution of diazomethane in ether until the solution is light yellow. After evaporation of the solvent chromatography of the residue (n-hexane/ethyl acetate = 2/1) gives the title compound as a colourless foam.

^{1}-NMR ($CDCl_3$):

5.14(d,J=7.5Hz,H-26);4.99(d,J=10Hz,H-20);
3.97(db,J=14Hz,H-6e);3.81(s,$COOCH_3$);2.70(m,H-11).

D) Compound of formula V (R_1 = R_2 = O-tBDMS; R_3 = CH_2-CH-CH_2; R_4 + R_{4a} = O; R_7 = OCH_3; R_9= CH_3; R_{1a} = R_{2a} = H; ⎯⎯ = sb; n = 2; diastereoisomer C)

Using 24,33-bis-O-tBDMS-FK506 as starting material and proceeding analogously as described in C) gives the title compound as a colourless foam.

E) Compound of formula V (R_1 = R_2 = O-tBDMS; R_3 = C_2H_5; R_4 + R_{4a} = O; R_7 = OCH_3; R_9 = CH_3; R_{1a} = R_{2a} = H; ⎯⎯ = sb; n = 2; diastereoisomer A)

2 g of calcium hydroxide are added to a solution of 3 g of 24,33-bis-O-tBDMS-FR 520 in 60 ml of tetrahydrofuran and 15 ml of water and stirred for 60 minutes at room temperature. Then the reaction mixture is partitioned between 0.5 N hydrochloric acid and ethyl acetate, the phases are separated, the organic phase is dried and evaporated under vacuum. The residue is redissolved in 30 ml of dichloromethane and triturated with a 1 M solution of diazomethane in ether until the solution is light yellow. After evaporation of the solvent chromatography of the residue (n-hexane/ethyl acetate = 2/1) gives the title compound as a colourless foam.

^{1}H-NMR ($CDCl_3$) mixture of rotamers = 58/42):

main rotamer:	5.20(d,J=7.5Hz,H-26); 4.93(d,J=10Hz,H-20);
	4.04(db,J=13Hz,H-6e);3.83(s,$COOCH_3$).
secondary rotamer:	5.13(d,J=10Hz,H-26); 4.70(d,J=10Hz,H-20);
	4.57(db,J=13Hz,H-6e); 3.63(s,COOCH3).

F) Compound of formula V (R_1 = R_2 = O-tBDMS; R_3 = CH_2-CH=CH_2; R_4 + R_{4a} = O; R_7 = OCH_3; R_9 = CH_3; R_{1a} = R_{2a} = H; ⎯⎯ = sb; n = 2; diastereoisomer A)

Using 24,33-bis-O-tBDMS-FK506 as starting material and proceeding analogously as described in E) gives the title compound as a colourless foam.

G) Compound of formula IV (R_1 = O-tBDMS; R_{1a} = R_{2a} = R_{4a} = H; R_2 + R_4 = O-CO-O; R_3 = C_2H_5; ═══ = sb; n = 2)

Using the compound of formula IV (R_1 = O-tBDMS; R_{1a} = R_{2a} = R_{4a} = H; R_2 = R_4 = OH; R_3 = C_2H_5; ═══ = sb; n = 2) as starting material and proceeding analogously as described in Example 13 the title compound is obtained as a colourless foam.

^{1}H-NMR-Spectra
(500 MHz)

Example:	spectrum:
1a	5.32 (d, J=8.9Hz, H-29); 4.88 (sb, H-26); 4.80 (db, J=7.6Hz, H-20); 4.09 (db, J=13Hz, H-6e); 4.03 (dxd, J=2.9/9.4Hz, H-14); 4.49 (sb, H-24); 3.38/3.33/3.32 (3xOCH$_3$).
1b, 2a	5.37 (d, J=9.1Hz, H-29); 5.155 (d, J=10.6Hz, H-26); 4.62 (d, J=10.6Hz, H-20); 4.11 (dxd, J=3.2/10.4Hz, H-24); 4.015 (dxd, J=4.7/13.3Hz, H-6e); 3.76 (d, J=8.5 Hz, H-14); 3.42/3.375/3.370 (3xOCH$_3$); 3.18 (dxt, J=3.6/13.3Hz, H-6a).
1c, 2b	5.24 (d, J=9Hz, H-29); 5.165 (d, J=7.2Hz, H-26); 4.86 (d, J=10Hz, H-20); 4.27 (dxd, J=5/13Hz, H-6e); 4.155 (m, H24); 3.68 (txd, J=8/2Hz, H-14); 3.504/3.406/3.404 (3xOCH$_3$); 3.24 (txd, J=13/3Hz, H-6a); 3.185 (m, H-21); 2.955 (m, H-32); 2.76 (dxdxd, J=2,5/11/16Hz, H-12); 2.67 (dxd, J=7/17Hz, H-23).
1d	5.39 (d, J=8.3Hz, H-29); 5.09 (d, J=10.5Hz, H-26); 4.84 (d, J=10.1Hz, H-20); 4.37 (dxd, J=4.2/12.7Hz, H-6e); 4.13 (m, H-24); 3.40/3.36/3.35 (3xOCH$_3$).
1e, 10	5.37 (dxq, J=9/1.3Hz, H-29); 5.18 (d, J=10.7Hz, H-26); 4.73 (d, J=10.8Hz, H-20);4.37 (dxd, J=4.9/13.3Hz, H-6e); 4.12 (dxd, J=4.4/11.1Hz; H-24); 3.60/3.41/3.39 (3xOCH$_3$).
3a	5.73 (dxdxt, J=10.2/17.1/7Hz, H-37); 5.31 (d, J=9.1Hz, H-29); 5.02 (dxq, J=17.1/1.8Hz, H-38tr.); 4.94 (dxq, J=10.2/1.8Hz, H-38cis); 4.88 (s, H-26); 4.80 (d, J=9Hz, H-20); 4.54 (sb, H-24); 4.09 (db, J=13Hz, H-6e); 4.02 (dxd, J=2.7/9.4Hz, H-14); 3.38/3.34/3.21 (3xOCH$_3$).
3b, 12b	5.71 (dxdxt, J=10.2/17.1/6.9Hz, H-37); 5.37 (d, J=8.2Hz, H-29); 5.175 (d, J=10.8Hz, H-26); 5.025 (dxq, J=17.1/1.8Hz, H-38tr.); 4.98 (dxq, J=10.2/1.8Hz, H-38cis); 4.655 (d, J=10.7Hz, H-20); 4.11 (dxd, J=3/10.6Hz, H-24); 4.015 (dxd, J=4.4/13.2Hz, H-6e); 3.755 (d, J=8.5Hz, H-14); 3.18 (dxt, J=3.7/13.2Hz, H-6a).

3c[2] 12a[2]	5.74 (dxdxt, J=10/17/7Hz, H-37); 5.25 (d, J=9Hz, H-29); 5.17 (d, J=7Hz, H-26) 5.09 (dxd, J=2/17Hz, H-38tr.); 4.99 (dxd, J=2/10Hz, H-38cis); 4.89 (d, J=10Hz, H20); 4.28 (dxd, J=4/13Hz, H-6e); 4.15 (m, H-24); 3.70 (t, H-14); 3.52/2x3.42 (3xOCH_3); 3.26 (txd, J=13/3Hz, H-6a); 2.97 (m, H-32).
3d , 11	5.71 (dxdxt, J=10.1/17.1/7.0Hz, H-37); 5.37 (d, J=9Hz, H-29); 5.18 (d, J=10.6Hz, H-26); 5.04 (dxq, J=17.1/1.9Hz, H-38tr.); 4.99 (dxq, J=10.1/1.9Hz, H-38cis); 4.75 (d, J=10.9Hz, H-20); 4.36 (dxd, J=4.8/13.3, H-6e); 4.12 (dxd, J=4.2/11Hz, H-24); 3.59/3.40/3.38 (3xOCH_3).
4[2]	5.31 (d, J=9Hz, H-29); 4.31 (dxdxd, J=5/8/11Hz, H-33); 4.03 (dxd, J=3/10Hz, H-14); 3.40/3.36/3.23 (3xOCH_3); 3.06 (s, O-mesyl).
5[2]	5.73 (dxdxt, J=10/17/7Hz, H-37); 5.30 (d, J=9Hz, H-29); 5.03 (dxq, J=17/2Hz, H-38tr.); 4.96 (dxq, J=10/2Hz, H-38cis); 4.51 (m, H-24); 4.31 (m, H-32); 4.02 (dxd, J=3/9.5Hz, H-14); 3.40/3.36/3.22 (3xOCH_3); 3.06 (s, O-mesyl).
6a , 74	5.27 (d, J=9.1Hz, H-29); 5.09 (s, H-26); 5.12 (d, J=10Hz, H-20); 4.08 (db, J=13Hz, H-6e); 4.02 (dxd, J=5.5/9.5Hz, H-14); 3.99 (m, H-24); 3.43/3.38/3.33 (3xs, 3xOCH_3).
6b , 72	5.33 (d, J=7Hz, H-26); 5.31 (d, J=9Hz, H-29); 4.79(d, J=10Hz, H-20); 2.91 (dxd, J=7/16Hz, H-23a).
6c , 73	5.12 (d, J=9Hz, H-29); 5.115 (d, J=3Hz, H-26); 5.00 (d, J=10Hz, H-20); 4.30 (dxd, J=4/13Hz, H-6e); 3.87 (m, H-24); 3.52 (t, H-14); 3.175 (m, H-21); 3.03 (m, H-32); 3.46/3.42/3.39 (3xs, 3xOCH_3).
6d[2] 71[2]	5.36 (d, J=9Hz, H-29); 5.18 (d, J=9Hz, H-26); 4.80 (d, J=10Hz, H-20); 4.38 (d, J=13Hz, H-6e); 4.01 (m, H-24); 3.50/3.42/3.38 (3xOCH_3).
6e[7], 75[7]	5.36(d;J=9Hz;H-29); 5.18(d;J=9Hz;H-26); 4.80(d;J=10Hz;H-20); 4.38(d;J=13Hz;H-6equ.); 3.38/3.42/3.50(3xs;3x-OCH_3).
7c[2], 78[2]	5.70 (dxdxt, J=10/17/7Hz, H-37); 4.30 (dxd, J=4/13Hz, H-6e); 3.87 (m, H-24); 3.54 (t, H-14); 3.03 (m, H-32); 3.47/3.42/3.39 (3xs, 3xOCH_3);
9b, 15	4.48 (dxdxd, J=12.5/2.6/0.8Hz, H-22); 4.27 (dxdb, J=4.5/13Hz, H-6equ.); 3.94 (dxdxd, J=10.1/3.4/0.6Hz, H-24); 3.42/3.408/3.39 (3xs, 3xOCH_3); 3.32 (m, H-14); 3.12 (txd, J=8.8/2.4Hz, H-13); 2.97 (m, H-32); 2.90 (d, J=9.2Hz, H-14).

13	5.38 (H-29); 4.91 (H-20 and H-26); 4.33 (H-24); 4.11 (db, J=13Hz, H-6e); 4.04 (dxd, J=2.6/9.5Hz, H-14); 3.39/3.34/3.30 (3xs, 3xOCH_3).
14	5.33 (d, J=9.1Hz, H-29); 5.26 (d, J=10.8Hz, H-26); 4.77 (d, J=10.4Hz, H-20); 4.13 (dxd, J=3.9/13.5Hz, H-6e); 4.08 (dxd, J=2.9/10.8Hz, H-24); 1.44 (d, J=6.9Hz, 11-CH_3).
19	5.28 (db, J=8.4Hz, H-29); 5.15 (db, J=7Hz, H-26); 4.78 (sb; H-20); 2.95 (m, H-32).
20	5.32 (d, J=8.9Hz, H-29); 5.27 (d, J=5.7Hz, H-26); 4.91 (d, J=10Hz, H-20); 3.98 (d, J=4.2Hz, H-10); 1.38 (d, J=6.8Hz, 11-CH_3).
21	5.37 (d, J=9Hz, H-29); 5.12 (d, H=10.5Hz, H-26); 4.68 (d, J=10.5Hz, H-20); 4.19 (d, J=7.3Hz, H-10); 4.10 (dxd, J=4.5/10.5Hz, H-24); 3.97 (dxd, J=3.5/13Hz, H-6e); 3.51/3.43/3.39 (3xs, 3xOCH_3); 2.96 (dxdxd, J=4.5/8.5/11.3Hz, H-32); 1.83 (d, J=1Hz, 19-CH_3); 1.59 (d, J=1.2Hz, 28-CH_3); 1.33 (d, J=7Hz, 11-CH_3); 0.83 (t, J=7Hz, H-37); 0.77 (d, J=6.5Hz, 25-CH_3).
22	5.36 (d, J=9,1Hz, H-29); 5.17 (d, J=9.9Hz, H-20); 4.85 (s, H-26); 4.00 (dxd, J=3.7/13Hz, H-6e); 3.95 (m, H-22); 3.88 (dxdxd, J=2.1/4.8/10.4; H-15 or H-24); 3.66 (dxd, J=2.1/11Hz, H-24 or H-15); 3.40/3.37/3.30 (3xs, 3xOCH_3); 3.26 (dxt, J=5.1/9.9Hz, H-13); 2.93 (dxdxd, J=5/8/11Hz, H-32).
27[4)]	5.24 (d, J=9Hz, H-29); 5.14 (d, J=4.2Hz, H-26); 5.0 (d, J=10Hz, H-20); 4.42 (db, J=5.8Hz, H-6equ.).
29	5.34 (d, J=9Hz, H-29); 5.10 (d, J=9.8Hz, H-26); 4.64 (d, J=10.5Hz, H-20); 4.31 (dxd, J=4/13Hz, H-6e); 4.09 (dxd, J=4.8/10Hz, H-24); 3.58 (15-OCH_3); 3.39 (32-OCH_3); 3.30 (13-OCH_3); 3.16 (9-OCH_3); 1.82 (19-CH_3); 1.51 (28-CH_3); 1.18 (d, J=7Hz, 11-CH_3).
30	5.42 (H-29); 4.99 (H-20); 4.84 (H-26); 4.03 (db, J=12Hz, H-6e); 2.97 (m, H-32).
31	5.38 (d, J=9Hz, H-29); 5.12 (d, J=10.5Hz, H-26); 4.74 (d, J=10.7Hz, H-20); 4.45 (dxd, J=3/13Hz, H-6e); 4.12 (dxd, J=4.4/10.2Hz, H-24); 3.58/3.40/3.37/3.17 (4xs, 4xOCH_3).
32a	5.37 (d, J=9Hz, H-29); 4.93 (d, J=11Hz, H-26); 4.65 (d, J=10Hz, H-20); 4.34 (dxd, J=3/13Hz, H-6e); 4.13 (dxd, J=3/11Hz, H-24); 5.44 (dxd, J=2/8Hz, H-14); 2x3.45/3.42 (2xs, 3xOCH_3); 2.97 (m, H-32).

32b	5.33 (d, J=8Hz, H-29); 5.11 (d, J=10.6Hz, H-26); 4.60 (d, J=10.6Hz, H-20); 4.25 (dxd, J=3.5/13.3Hz, H-6e); 4.11 (dxd, J=3.4/10.6Hz, H-24); 5.48 (d, J=8.9Hz, H-14); 3.42/3.40/3.37 (3xs, 3xOCH_3); 2.97 (m, H-32).
32c	5.47 (d, J=9Hz, H-29); 5.11 (d, J=11Hz, H-26); 4.58 (d, J=10Hz, H-20); 4.25 (dxd, J=3/13Hz, H-6e); 4.08 (dxd, J=3/11Hz, H-24); 3.60 (d, J=8Hz, H-14); 3.55/3.41/3.35 (3xs, 3xOCH_3); 2.98 (m, H-32).
32d	5.42 (d, J=9Hz, H-29); 5.25 (b, H-26); 4.59 (d, J=10Hz, H-20); 4.18 (H-6e); 4.11 (dxd, J=3/10Hz, H-24); 3.43/3.39/3.37 (3xs, 3xOCH_3).
33	8.20/7.48/7.09 (imidazolyl-H); 5.37 (d, J=8.9Hz, H-29); 5.27 (dxd, J=2/8.8Hz, H-14); 4.88 (d, J=10.5Hz, H-26); 4.62 (d, J=10.3Hz, H-20); 4.34 (dxd, J=4.2/13.4Hz, H-6); 4.12 (dxd, J=3.5/10.2Hz, H-24); 2x3.42/3.48 (2xs, 3xOCH_3).
34	5.37 (d, J=9Hz, H-29); 5.17 (dxd, J=3/8Hz, H-14); 5.10 (d, J=10.3Hz, H-26); 4.74 (d, J=10.7Hz, H-20); 4.37 (dxd, J=4.6/13.1Hz, H-6e); 4.11 (dxd, J=4.2/11Hz, H-24); 2x2.13 (1xs, 2x$COCH_3$); 3.45/3.41/3.38 (3xs, 3xOCH_3).
35a	5.38 (d, J=9.1Hz, H-29); 4.76 (d, J=10.8Hz, H-20); 4.43 (dxd, J=3/13Hz, H-6e); 4.13 (dxd, J=4/10Hz, H-24); 3.55/3.41/3.40 (3xs, 3xOCH_3):
35b	5.39 (d, J=8.9Hz, H-29); 5.13 (d, J=10.4Hz, H-26); 4.79 (d, J=10.1Hz, H-20); 4.14 (m, H-24); 3.46/3.42/3.39 (3xs, 3xOCH_3).
36a[2]	5.39 (d, J=9.5Hz, H-29); 5.05 (d, J=10.4Hz, H-26); 4.95 (dxd, J=2/8Hz, H-14); 4.73 (d, J=10.7Hz, H-20); 4.38 (dxd, J=3/13Hz, H-6e); 4.12 (m, H-24); 3.56/3.45/3.39/3xs, 3xOCH_3); 3.25/3.13 (2xs, 2xCH_3SO_2-).
36b[2]	5.38 (d, J=8.5Hz, H-29); 5.17 (d, J=10.5Hz, H-26); 4.96 (dxd, J=2/8Hz, H-14); 4.73 (d, J=11.5Hz, H-20); 4.35 (dxd, J=3/13Hz, H-6e); 4.12 (m, H-24); 3.59 /3.41/3.40 (3xs, 3xOCH_3); 3.11 (s, CH_3SO_2-).
37a	5.43 (d, J=8.7Hz, H-29); 5.03 (m, 2H, H-14 and H-26); 4.57 (d, J=10,1Hz, H-20); 4.20 (dxd, J=13.6/4.7Hz, H-6e); 4.06 (dxd, J=11.8/3.3Hz, H-24); 3.52/3.39/3.30 (3xs, 3xOCH_3); 2.16/2.13 (2xs, 2xOAc).
37b	5.34 (d, J=9Hz, H-29); 5.17 (dxd, J=7.2/3.6Hz, H-14); 4.94 (d, J=9.8Hz, H-26); 4.65 (d, J=9.8Hz,H-20); 4.30 (dxd, J=13.6/4.5Hz, H-6e); 4.11 (dxd, J=10/3.6Hz, H-24).

37c	5.43 (d, J=9Hz, H-29); 5.03 (d, J=10.7Hz, H-26); 4.61 (d, J=10.5Hz, H-20); 4.21 (dxd, J=13.5/4.6Hz, H-6e); 4.07 (dxd, J=10.7/3.3Hz, H-24); 3.61/3.40/3.33 (3xOCH_3); 2.11 (s, OAc).
37d	5.4 (d;J=9.2Hz;H-29); 5.02 (sb;H-26); 4.58 (db;J=10Hz;H-20).
39	5.44/5.04/4.57 (3xd, J=8.2/10.8/10.1Hz, H-29/26/20); 3.74 (s, -$COOCH_3$); 3.54/3.41/3.22 (3xs, 3xOCH_3).
41	7.93 (d, J=1Hz, CHO); 5.53/5.28/4.86 (3xd, J=7.9/10.4/10.6Hz, H-29/26/20); 4.37 (dxd, J=13.3/4.7Hz, H-6equ.); 4.08 (m, H-24).
43	5.38 (d, J=9.9Hz, H-29); 5.1 (d, J=10.4Hz, H-26); 4.73 (d, J=10.8Hz, H-20); 4.4 (dxd, J=13.2/4.7Hz, H-6equ.); 4.12 (dxd, J=7.1/4.1Hz, H-24); 1.41 (s, BOC).
44	5.43 (d, J=8.9Hz, H-29); 4.98 (d, J=10.8Hz, H-26); 4.58 (d, J=10.4Hz, H-20); 4.22 (m, H-6equ.); 4.07 (dxd, J=3.3/10.9Hz, H-24); 3.54/3.41/3.23 (3xs, 3xOCH_3).
45[5)]	5.48 (dxd, J=1/8.9Hz, H-29); 4.66 (d, J=10.2Hz, H-20); 4.21/4.14 (db/dxd; H-6equ./H-24).
50	mixture: ketone/hemiketal = 40/60 ketone: 5.37 (d, J=8.9Hz, H-29); 4.96 (d, J=10.7Hz, H-26); 4.62 (d, J=10.5Hz, H-20); 4.46 (d, J=10.4Hz, H-15); 4.12 (dxd, J=10.5/3.3Hz, H-24). hemiketal: 5.05 (d, J=8.9Hz, H-29); 5.11 (d, J=3.5Hz, H-26); 4.81 (d, J=10.2Hz, H-20); 3.51 (dxd, J=9.1/2.8Hz, H-15); 3.77 (dxd, J=11.7/4.6Hz, H-13); 3.56 (m, H-24).
51	5.38 (d, J=9.0Hz, H-29); 5.22 (d, J=10.2Hz, H-26); 4.79 (d, J=10.7Hz, H-20); 4.41 (dxd, J=11.9/3.2Hz, H-13); 4.38 (dxd, J=13/4Hz, H-6e); 4.15 (dxd, J=10.7/4.3Hz, H-24); 4.08 (dxd, J=9.2/3.5Hz, H-15); 3.42/3.40/3.37 (3xs, 3xOCH_3); 3.23 (dxdxd, J=10.9/8.5/5.6Hz, H-21); 3.17 (txd, J=13.2/3.6Hz, H-6a).
52	mixture: ketone/hemiketal = 40/60 ketone: 5.38 (d, J=9Hz, H-29); 4.92 (d, J=10.7Hz, H-26); 4.60 (d, J=10Hz, H-20); 4.47 (d, J=9.5Hz, H-15). hemiketal: 5.08 (d, J=9Hz, H-29); 5.11 (d, J=4.2Hz, H-26); 4.83 (d, J=10Hz, H-20); 3.76 (dxd, J=11.6/4.6Hz, H-13).
58a	5.4 (dxd, J=8.9/1.1Hz, H-29); 5.12 (d, J=10.8Hz, H-26); 4.57 (db, J=10.5Hz, H-20); 4.24 (dxd, J=13.6/4.8Hz, H-6equ.); 4.07 (dxd, J=11/3.5Hz, H-24); 3.63 (d, J=8.5Hz, H-14); 3.52/3.40/3.21 (3xOCH_3).

58b	5.34 (dxd, J=8.9/1.1Hz, H-29); 4.89 (d, J=10.2Hz, H-26); 4.62 (d, J=10.3Hz, H-20); 4.3 (dxd, J=4.3/13.8Hz, H-6equ.); 2.94 (m, H-32); 2.84 (dxd, H-23a).
60a	5.32 (d; J=9Hz, H-29); 5.18 (d, J=9.1Hz, H-26); 4.85 (d, J=10.4Hz, H-20); 4.37 (db, J=10.4Hz, H-6equ.); 4.16 (m, H-24); 3.44/3.41/3.36 (3xs, 3xOCH_3).
60b	5.34 (d, J=9Hz, H-26); 5.22 (d, J=9.9Hz, H-29); 4.92 (d, J=10,4Hz, H-20); 4.36 (db, J=11Hz, H-6equ.); 4.11 (m, H-24); 3.40/3.38/3.36 (3xs, 3xOCH_3).
61	5.35 (d, J=9Hz, H-29); 4.88 (sb, H-26); 4.81 (d, J=8.2Hz, H-20); 4.53 (H-24); 4.11 (db, J=13Hz, H-6e); 4.03 (dxd, J=2.8/9.5Hz, H-14); 3.40/3.34/3.23 (3xs, 3xOCH_3).
62[2]	5.74 (dxdxt, J=10/17/7Hz, H-37); 5.34 (d, J=9Hz, H-29); 4.80 (d, J=9Hz, H-20); 4.54 (H-24); 4.02 (dxd, J=2.5/10Hz, H-14); 3.41/3.34/3.22 (3xs, 3xOCH_3).
63[2]	5.72 (dxdxt; J=10/17/7Hz, H-37); 5.41 (d, J=9Hz, H-29); 5.18 (d, J=10.5Hz, H-26); 5.04 (dxq, J=17/2Hz, H-38tr.); 4.98 (dxq, J=10/2Hz, H-38cis); 4.65 (d, J=10Hz, H-20); 4.12 (dxd, J=3/11Hz, H-24); 4.04 (dxd, J=3/13Hz, H-6e); 3.19 (dxt, J=3/13Hz, H-6a); 3.02 (m, H-32).
64[2]	5.75 (dxdxt, J=10/17/7Hz, H-37); 5.28 (d, J=9Hz, H-29); 5.17 (d, J=7Hz, H-26); 5.09 (dxd, J=2/17Hz, H-38tr.); 4.98 (dxd, J=2/10Hz, H-38cis); 4.88 (d, J=10Hz, H-20); 4.28 (dxd, J=4/13Hz, H-6e); 4.15 (m, H-24); 3.70 (t, H-14); 2x3.42/3.52 (2xs, 3xOCH_3); 3.25 (txd, J=13/3Hz, H-6a); 3.03 (m, H-32).
65	5.43 (d, J=8.8Hz, H-29); 4.97 (d, J=9.5Hz, H-20); 4.82 (H-26); 4.30 (H-24); 4.04 (db, J=13Hz, H-6e); 3.79/3.41/3.35/3.33 (4xs, 4xOCH_3).
67	8.20/7.48/7.08 (imidazolyl-H); 5.37 (d, J=9Hz, H-29); 5.26 (dxd, J=1.9/8.9Hz, H-14); 4.86 (d, J=10.6Hz, H-26); 4.60 (d, J=10.3Hz, H-20); 4.34 (dxd, J=4.5/13.6Hz, H-6e); 4.12 (dxd, J=3.3/10.2Hz, H-24); 3.48/3.42/3.41 (3xs, 3xOCH_3).
68	mixture: ketone/hemiketal = 60/40 ketone: 5.38 (d, J=9Hz, H-29); 4.98 (d, J=10.5Hz, H-26); 4.66 (d, J=10.3Hz, H-20); 4.46 (d, J=8.9Hz, H-15). hemiketal: 5.11 (d, J=9Hz, H-29); 5.13 (d, J=4.4Hz, H-26); 4.87 (d, J=10Hz, H-20); 3.76 (dxd, J=11.4/4.4Hz, H-13).
69a	5.36 (d, J=8.2Hz, H-26); 4.86 (db, J=10Hz, H-29); 4.31 (dxd, J=13.3/4.3Hz, H-6equ.); 4.1 (dxd, J=10,2/3.6Hz, H-24); 3.54/3.41/3.32 (3xs, 3xOCH_3).

69c	5.38/5.18/4.71 (3xd, J=8.5/9.1/10.4Hz, H-26/29/20); 3.58/3.42/3.31 (3xs, 3xOCH_3).
69d	5.42/5.13/4.59 (3xd, J=9.8/10.8/10.6Hz, H-29/26/20); 4.08 (dxd, J=11/3.5Hz, H-24); 3.6/3.39/3.32 (3xs, 3xOCH_3).
80[2)]	4.35 (dxdxd, J=5/8/11Hz, H-33); 3.41/3.37/3.34 (3xs, 3xOCH_3); 3.07 (s, CH_3SO_2-).
81[2)]	5.73 (dxdxt, J=10/17/7Hz, H-37); 5.22 (d, J=9Hz, H-29); 4.34 (m, H-33); 3.41/3.36/3.33 (3xs, 3xOCH_3); 3.08 (s, CH_3SO_2-).
82	5.20 (s, H-26); 5.17 (d, J=9Hz, H-29); 4.98 (d, J=9.7Hz, H-20); 4.12 (H-6e); 4.10 (d, J=4.6Hz, H-10); 4.04 (m, H-24); 3.40/3.36/3.30 (3xs, 3xOCH_3); 1.685 (d, J=1Hz, 28-CH_3); 1.66 (d, J=1Hz, 19-CH_3); 1.28 (d, J=6.7Hz, 11-CH_3); 0.99 (d, J=6.5Hz, 17-CH_3); 0.955 (d, J=7Hz, 25-CH_3); 0.86 (t, J=7.4Hz, H-37).
83	5.10 (d, J=9Hz, H-29); 5.12 (s, H-26); 4.94 (d, J=9.5Hz, H-20); 4.09 (db, J=13Hz, H-6e); 3.94 (d, J=3Hz, H-10); 3.73 (m, H-24); 3.41/3.35/3.33 (3xs, 3xOCH_3); 1.64 (d, J=1Hz, 28-CH_3); 1.58 (d, J=1Hz, 19-CH_3); 1.40 (d, J=6.8Hz, 11-CH_3); 0.99 and 0.99 (d and d, J=7 and 7Hz, 17-CH_3 and 25-CH_3); 0.87 (t, J=7.4Hz, H-37).
84[3)]	5.22 (d, J=9Hz, H-29); 5.04 (d, J=6.6Hz, H-26); 4.80 (d, J=10Hz, H-20); 4.15 (s, H-10); 4.00 (m, H-24); 3.94 (dxd, J=3/13Hz, H-6e); 3.47/3.43/3.41 (3xs, 3xOCH_3); 3.05 (dxdxd, J=4.3/8.8/11.3Hz, H-32); 2.85 (dxd, J=7.9/16.7Hz, H-23a); 2.51 (dxd, J=5.1/16.7Hz, H-23b); 2.32 (m, H30); 1.74 (d, J=1Hz, 19-CH_3); 1.63 (d, J=1Hz, 28-CH_3); 1.29 (d, J=7Hz, 11-CH_3); 0.85 (t, J=7.4Hz, H-37).
85	5.27 (s, H-26); 5.16 (d, J=9.1Hz, H-29); 5.13 (d, J=9.5Hz, H-20); 4.07 (dxd, J=4.9/13.5Hz, H-6e); 3.95 (m, H-24); 3.90 (m, H-22); 3.62 (dxdxd, J=2.4/4.4/8.2Hz, H-15); 3.54 (dxd, J=2.3/9.5Hz, H-14); 3.23 (dxt, J=5/10Hz, H-13); 3.41/3.40/3.38 (3xs, 3xOCH_3); 1.70 (d, J=1Hz, 28-CH_3); 1.58 (s, 19-CH_3); 1.10 (d, J=7Hz, 11-CH_3); 0.98 (d, J=7Hz, 25-CH_3); 0.95 (d, J=7Hz, 17-CH_3); 0.89 (t, J=7.5Hz, H-37).
86	5.28 (d, H-29); 5.27 (s, H-26); 5.17 (d, J=10.1Hz, H-20); 3.94 (db, J=13Hz, H-6e); 3.8 (m, H-24); 3.58 (dxd, J=5.7/9.5Hz, H-14); 3.81 (s, 9-OCH_3); 3.50 (s, 15-OCH_3); 3.41 (s, 32-OCH_3); 3.34 (s, 13-OCH_3); 3.10 (dxdxd, J=2.5/6/10Hz, H-15); 3.02 (dxdxd, J=4.3/8.8/11.2Hz, H-32); 2.30 (dxt, J=3.6/13Hz, H-6a); 1.75 (d, J=1Hz, 19-CH_3); 1.69 (d, J=1,1Hz, 28-CH_3). 1.16

(d, J=6.9Hz, 11-CH_3). 1.10 (d, J=7Hz, 25-CH_3). 0.99 (d, J=6.4Hz, 17-CH_3); 0.89 (t, J=7.4Hz, H-37).

87 5.23 (d, J=9Hz, H-29); 5.19 (d, J=5.2Hz, H-26); 4.95 (d, J=10Hz, H-20); 4.38 (dxd, J=4/13Hz, H-6e); 3.55/3.40/3.31/3.12 (4xs, 4xOCH_3).

88[2)] 5.30 (d, J=9Hz, H-29); 5.02 (d, J=8.2Hz, H-26); 4.83 (d, J=9.7Hz, H-20); 4.48 (dxd, J=3/13Hz, H-6e); 3.97 (m, H-24); 2x3.40/3.22/3.19 (3xs, 4xOCH_3).

89 5.28 (d, J=9Hz, H-29); 5.25 (d, J=6Hz, H-26); 4.84 (d, J=10Hz, H-20); 4.30 (dxd, J=3/13Hz, H-6e); 4.02 (m, H-24); 3.71 (d, J=8Hz, H-14); 3.04 (m, H-32); 3.59/3.44/3.38 (3xs, 3xOCH_3).

90[2)] 5.32 (d, J=8.7Hz, H-29); 5.22 (d, J=6.8Hz, H-26); 4.77 (d, J=10.3Hz, H-20); 4.29 (db, J=13Hz, H-6e); 4.03 (m, H-24); 5.45 (d, J=8.6Hz, H-14); 3.44/3.43/3.38 (3xs, 3xOCH_3).

91 8.20/7.48/7.08 (imidazolyl-H); 5.22 (d, J=9.1Hz, H-29); 5.31 (dxd, J=2.8/8.2Hz, H-14); 5.09 (d, J=6.0Hz, H-26); 4.88 (d, J=9.7Hz, H-20); 4.31 (dxd, J=3/12Hz, H-6e); 4.08 (m, H-24); 2x3.43/3.41 (2xs, 3xOCH_3).

92 mixture: ketone/hemiketal = 34/66
ketone: 5.25 (d, J=9Hz, H-29); 5.07 (d, H-26); 4.84 (d,J=9.7Hz, H-20).
hemiketal: 5.04 (d, J=9Hz, H-29); 5.15 (s, H-26); 4.76 (d, H-20); 3.57 (dxd, J=9.8/2.6Hz, H-15); 3.75 (dxd, J=11.7/4.6Hz, H-13).

93 mixture: ketone/hemiketal = 1/1.8
ketone: 5.25 (d, J=9.2Hz, H-29); 5.08 (d, J=6.6Hz, H-26); 4.85(d,J=9.6Hz, H-20).
hemiketal: 5.04 (d, J=9.3Hz, H-29); 5.15 (s, H-26); 4.76 (d, J=10.2Hz, H-20); 3.57 (dxd, J=10.1/2.4Hz, H-15); 3.76 (dxd, J=11.7/4.5Hz, H-13).

94 5.28 (d, J=9.1Hz, H29); 5.19 (d, J=5.9Hz, H26); 4.97 (d, J=9.7Hz, H20); 4.40 (m, H6e); 4.29 (dxd, J=8.9/4.5Hz, H13); 3.92 (t, J=7Hz, H15); 3.87 (m, H24); 3.41/3.39/3.38 (3xs, 3xOCH_3); 3.24 (m, H21).

95 5.28 (d, J=9.0Hz, H-29); 5.12 (d, J=7.9Hz, H-14); 5.10 (d, J=7.5Hz, H-26); 4.82 (d, J=10.4Hz, H-20); 4.23 (dxd, J=13/3Hz; H-6e); 4.02 (t, H24); 3.50/3.41/3.30 (3xs, 3xOCH_3); 2.15/2.06 (2xOAc).

96 5.20 (m, 2H, H-29 and H-14); 5.10 (d, J=6Hz, H-26); 4.90 (d, J=9.7Hz, H-20); 4.30 (dxd, J=13.3/4.5Hz, H-6e); 4.08 (m, H-24); 3.45/3.44/3.41 (3xs, 3xOCH_3); 3.20 (m, H-21); 2.12 (OAc).

97	5.28 (d, J=8.7Hz, H-29); 5.09 (d, J=7.2Hz, H-26); 4.85 (d, J=10.4Hz, H-20); 4.23 (dxd, J=13/3Hz, H-6); 4.05 (m, H-24); 3.59/3.41/3.33 (3xs, 3xOCH_3); 3.27 (m, H-21); 2.05 (s, OAc);
98	5.37 (d, J=5.4Hz, H-26); 5.32 (d, J=8.7Hz, H-29); 4.78 (d, J=10.2Hz, H-20); 4.16 (dxd, J=13/3Hz, H-6e); 4.00 (m, H-24); 3.42/3.38/3.36 (3xs, 3xOCH_3), 2.21 (s, OAc).
99	5.31 (d, J=9Hz, H-29); 5.19 (d, J=6Hz, H-26); 5.08 (dxd, J=5/7Hz, H-14); 4.80 (d, J=10Hz, H-20); 4.38 (dxd, J=13/3Hz, H-6e); 3.81 (m, H-24).
100	5.28 (d, J=9.1Hz, H-29); 4.96 (d, J=10.1Hz, H-20); 4.76 (d, J=4.8Hz, H-26); 4.21 (m, H-24); 3.99 (dxd, J=2.3/9.7Hz, H-14); 3.40/3.35/3.34 (3xs, 3xOCH_3); 3.02 (dxdxd, J=4.3/8.8/11.3Hz, H-32); 1.80 (d, J=1Hz, 19-CH_3); 1.74 (d, J=1.1Hz, 28-CH_3); 1.16 (d, J=7Hz, 11-CH_3); 0.94 (d, J=7Hz, 25-CH_3 and 17-CH_3); 0.87 (t, J=7.4Hz, H-37).
101	5.32 (d, J=9Hz, H-29); 5.23 (d, J=7.8Hz, H-26); 4.85 (d, J=10.2Hz, H-20); 4.17 (dxd, J=4/13.5Hz, H-6e); 4.02 (m, H-24); 3.60 (m, H-15); 3.51 (dxd, J=1.4/9.5Hz, H-14); 1.78 (d, J=1Hz, 19-CH_3); 1.44 (d, J=6.9Hz, 11-CH_3).
102[2)]	5.09 (sb, H-26); 4.99 and 4.91 (d and d; J=10 and 10Hz, H-20 and H-29); 4.33 (db, J=13Hz, H-6e); 3.66 (m, H-22); 3.57 (m, H-24); 3.43/3.38/3.36 (3xs, 3xOCH_3).
103	5.215/5.14/4.95 (3xd, J=9/5.4/10.2Hz, H-29/26/20); 4.28 (dxd, J=4.5/13.7Hz; H-6equ.); 3.64/3.58/3.41/3.32 (4xOCH_3).
104	5.28/5.06/4.87 (3xd, J=8.9/7.2/10.4Hz, H-29/26/20); 4.22 (db, J=13.5Hz, H-6equ.); 3.33/3.42/3.56 (3xs, 3xOCH_3).
105	6.44/7.82 (2xsb, 2xNH); 5.22 (sb, H-26); 5.15 (d, J=8.9Hz, H-29); 4.95 (d, J=9.2Hz, H-20); 4.53 (sb, H-6equ.); 4.18 (dxd, J=4.6/13.5Hz, H-24); 3.25(q, H-21); 3.15 (dxt, H-6a); 3.39/3.42/3.435 (3xs, 3xOCH_3).
106	5.26/5.08/4.88 (3xd, J=9.5/6.9/10.4Hz, H-29/26/20); 4.24 (dxd, J=4.4/13.5Hz, H-6equ.); 4.03 (tb, H-24); 3.56/3.41/3.33 (3xs, 3xOCH_3); 2.97/2.76 (2xs, 2xNCH_3).
107[5)]	5.32/5.13/4.97 /3xd, H-26/29/20); 3.95 (m, H-24); 3.36/3.39/3.42 (3xs, 3xOCH_3.
117	5.25/5.05 (2xd, H-26/29); 3.31/3.36/3.42 (3xs, 3xOCH_3); 3.03 (m, H-32).
118[6)]	5.2/5.02 (m/d, H-29/26/20); 4.38 (dxd, H-6equ.); 3.42/3.38/3.35 (3xs, 3xOCH_3).

^{13}C-NMR-Spectra
($CDCl_3$)

Example:	spectrum:
6f	212.32 (C-22), 202.22 (C-10), 170.27 (C-8), 165.04 (C-1), 139.26 (C-19), 133.22 (C-29), 130.93 (C-28); 123.57 (C-20); 84.466/84.145 (C-26/32), 78.475 (C-13), 77.588 (C-15), 76.573 (C-10), 73.478/73.451 (C-33/14), 72.14 (C-2), 66.9 (C-24), 58.816/57.042/56.483 (3xOCH_3), 54.493 (C-21), 46.995 (C-18), 45.819 (C-23).
7d	210.5/202.5/170.9/165.4/75.2(C-22/10/8/1/9).
7e, 79	210.1/205.8/172.8/165.9/78.2(C-22/10/8/1/9).
9a	170.12/169.72 (C-1/8), 150.4 (O.CO.O), 138.67 (C-19), 132.47 (C-28), 129.62 (C-29), 123.35 (C-20), 96.79 (C-9), 83.997 (C-32).
9c	201.70 (C-9), 170.14/165.05 (C-1/8), 149 (O.CO.O), 138.01 (C-19), 131.11 (C-29), 129.50 (C-28), 124.25 (C-20), 83.916 (C-32).
16	199.10 (C-10), 166.99/165.87 (C-1/8), 152.3/149.22 (O.CO.O), 138.28/131.02/129.68/124.16 (C-19/29/28/20), 84.126 ($OCme_3$), 83.992 (C-32), 80.535 (C-9), 79.17 (C-13), 78.237 (C-24), 77.892 (C-22), 77.524 (C-15), 77.01 (C-26), 73.671 (C-14), 73.384 (C-33), 72.137 (C-2), 57.495/56.934/56.551 (3xOCH_3), 49.047 (C-18), 44.062 (C-21), 38.118/37.531 (C-25/C-6), 35.071/34.636/34.39 (C-30/31/11), 32.647 (C-16), 31.094/30.797/30.584 (C-34/3/35); 27.97 (C-12), 27.58 (C-17), 25.673 (C-23), 24.65 (C-36), 23.304 (C-5), 21.875 (17-methyl), 20.818 (C-4), 17.362 (19-methyl), 14.783 (28-methyl), 13.223 (11-methyl), 11.929 (C-37); 9.26 (25-methyl).
17	167.86/166.00 (C-1/8), 152.41/149.72 (2xO.CO.O), 137.22/133.09/128.98/124.98 (C-19/29/28/20), 104.10 (C-9), 88.88 (C-10), 57.326/56.963/56.226 (3xOCH_3), 50.655 (C-18), 46.017 (C-25), 42.98 (C-21), 39.997 (C-6), 35.237 (C-30), 35.026 (C-16), 34.39 (C-12), 33.991 (C-31), 31.962 (C-11), 31.287/31.250 (C-23/34), 30.312 (C-35), 26.284 (C-3), 25.840 (C-36), 25.383 (C-17).
18	201.51 (C-10), 170.89 (C-1), 164.82 (C-8), 150.03 (O.CO.O), 137.85/131.44/129.65/124.84 (C-19/29/28/20).
23a	170.66/170.56 (C-1/8), 149.86 (O.CO.O), 138.30 (C-19), 130.39 (C-28), 129.80 (C-29), 123.91 (C-20), 84.226 (C-32), 80.051 (C-13), 79.23 (C-9), 78.966/78.904 (C-22/24).

23b 171.65/170.91 (C-1/8), 149.44 (O.CO.O), 138.44 (C-19), 130.20 (C-28), 129.36 (C-29), 123.80 (C-20), 84.138 (C-32), 81.238 (C-9), 80.48 (C-13), 79.403 (C-22), 79.111 (C-10), 78.927 (C-24), 77.25 (C-14), 76.994 (C-15), 75.947 (C-26).

24b 172.97 (C-1), 168.48 (C-8), 134.4 (C-19), 131.59 (C-28), 128.97 (C-29), 126.53 (C-20), 84.166 (C-32), 75.195 (C-33), 58.033/56.829/56.127 (3xOCH_3), 48.844 (C-18), 46.212 (C-21).

25 167.73/164.85 (C-1/8), 149.69 (O.CO.O), 136.79 (C-19), 132.39 (C-28), 132.39/130.73 (C-28/29), 128.53 (C-20), 84.111 (C-32), 57.693/56.820/56.472 (3xOCH_3).

26a 202.42 (C-9), 171.13 (C-1), 165.28 (C-8), 136.11 (C-19), 132.62 (C-29), 131.12 (C-28), 126.82 (C-20), 84.113 (C-32), 58.456 (OCH_3), 56.531 (2xOCH_3), 49.714 (C-18), 46.373 (C-23).

26b 173.74 (C-1), 168.91 (C-8), 137.50 (C-19), 131.73 (C-29), 128.58 (C-28), 126.33 (C-20), 84.208 (C-32), 57.2/57.061/56.676 (3xOCH_3).

28 201.2(C-10); 168.6 (C-1); 165.6 (C-8); 137.4 (C-19); 130.9 (C-28); 128.9 (C-20); 128.5 (C-29).

38 209.9/208.9/199.45/165.4/163.1(C-22/14/10/1/8) 159.04(-OCHO).

42 208.54 (C-22), 199.53 (C-10), 166.42 (C-1), 164.38 (C-8), 158.58 (OCHO), 140.28 (C-19), 137.73 (C-29), 130.79 (C-28), 123.57 (C-20), 86.243 (C-26), 84.057 (C-32), 76.9 (C-14), 75.069 (C-33), 73.417 (C-2).

46 209.27 (C-22), 199.20 (C-10), 167.64/163.74 (C-1/8), 154.47 (O.CO.N), 140.50/137.89/130.14/123.39 (C-19/29/28/20), 70.206 (C-2).

47a 210.32 (C-22), 167.78/167.16 (C-1/8), 155.54 (O.CO.N), 138.79 (C-19), 135 (b, C-29); 131.02 (C-28), 124.43 (C-20), 91.609 (C-10), 84.054 (C-32), 75.092 (C-33), 68.584 (C-24), 58.109/58.042/57.942 (3xOCH_3).

47b 208.65/200.42 (C-22/14), 167.39/164.83 (C-1/8), 154.24 (O.CO.N), 139.33 (C-19), 137.29 (C-29), 130.71 (C-28), 124.16 (C-20).

48 209.25 (C-22), 169.24 (C-1), 166.27 (C-8), 153.41 (O.CO.N), 140.69 (C-19), 140.29 (C-29), 129.40 (C-28), 122.82 (C-20), 87.968 (C-26), 90.905/86.991 (C-9/10), 84.261 (C-32), 61.503 (15-OCH_3), 58.071 (32-OCH_3), 56.677 (13-OCH_3).

49 209.14 (C-22), 184.68 (O.CS.N), 168.92 (C-1), 165.28 (C-8), 141.03 (C-19), 139.72 (C-29), 129.43 (C-28), 122.65 (C-20), 95.02 (C-10), 91.581 (C-9), 88.676 (C-26), 84.297 (C-32), 82.275 (C-13), 78.245 (C-15), 75.575/75.432 (C-33/14), 72.818 (C-2), 68.016 (C-24), 61.514 (15-OCH_3), 58.238 (32-OCH_3), 56.806 (13-OCH_3), 56.512 (C-21), 48.776 (C-23), 30.083 (N-methyl).

53 210.10/208.92/206.25 (C-22/10/14), 167.39/164.05 (C-1/8), 139.39/138.10/130.36/123.85 (C-19/29/28/20), 81.232 (C-9), 80.082 (C-15).

54 209.31/208.70/204.01 (C-22/10/14), 167.92/163.88 (C-1/8), 139.79/137.45/130.83/123.97 (C-19/29/28/20), 83.118 (C-10), 67.831 (C-24), 58.512/58.027/58.02/54.311 (4xOCH_3).

55 208.92 (C-22), 198.98 (C-10), 166.97/163.29 (C-1/8), 140.66/137.29/131.02/123.46 (C-19/29/28/20).

56 208.89 (C-22), 199.66 (C-10), 165.85/164.51 (C-1/8), 139.92/137.41/130.13/123.35 (C-20/29/28/20), 70.59 (C-2), 67.291 (C-24), 62.863 (C-9).

57 209.55 (C-22), 196.68 (C-10), 166.0/164.38 (C-1/8), 140.28/137.05/130.88/123.28 (C-19/29/28/20), 85.703 (C-26), 84.097 (C-32), 75.189 (C-33), 70.389 (C-2), 68.139 (C-24), 62.075 (C-9), 60.122/58.019/57.752 (3xOCH_3), 56.213 (C-21), 48.031 (C-23), 46.862 (C-18), 16.043 (19-methyl), 11.14 (28-methyl).

59 208.58 (C-22), 203.72 (C-10), 170.7 (C-1), 163.86 (C-8), 140.39/137.51/130.96/123.69 (C-19/29/28/20), 86.028 (C-26), 84.051 (C-32), 80.267 (C-15), 79.691 (C-13), 76.424 (C-9), 75.118 (C-33), 73.368 (C-14), 72.925 (C-2), 68.033 (C-24), 61.289/57.928/55.55 (3xOCH_3), 56.357 (C-21), 47.658 (C-18), 47.291 (C-23).

66 209.5/204.6/167.5/164.3/81.5(C-22/10/1/8/9).

69b	209.62 (C-22), 204.50 (C-10), 169.09/164.71 (C-1/8), 140.61/135.79/130.8/123.44 (C-19/29/28/20), 77.56 (C-9), 71.403 (C-2).
108	211.33 (C-22), 199.36 (C-10), 166.71/164.47 (C-1/8), 139.03/133.59/130.73/124.90 (C-19/29/28/20), 85.405 (C-26), 84.14 (C-32), 78.99 (C-13), 77.963 (C-15), 75.699 (C-14), 73.466 (C-33), 72.245 (C-2), 67.223 (C-24), 64.425 (C-9), 57.521/56.865/56.522 (3xOCH_3), 55.062 (C-21), 9.094 (25-methyl).
109	211.81/197.45 (C-22/10), 165.0/164.76 (C-1/8), 138.26/131.68/130.93/123.37 (C-19/29/28/20), 62.723 (C-9), 9.371 (25-methyl).
110	210.07/209.53/205.85 (C-22/14/10), 167.32/164.52 (C-1/8), 139.69/135.58/130.53/123.81 (C-19/29/28/20), 81.337 (C-9), 72.293 (C-2), 8.58 (25-methyl).
111	211.37/206.86/203.55 (C-22/14/10), 167.76/164.71 (C-1/8), 138.96/134.31/130.30/124.64 (C-19/29/28/20).
112	200.24 (C-10), 167.81/166.31 (C-1/8), 149.01 (O.CO.O), 138.54 /129.73/129.13/123.57 (C-19/29/28/20), 74.637 (C-9), 11.737 (C-37), 10.257 (25-methyl).
113	201.74 (C-10), 170.16/165.04 (C-1/8), 149.25 (O.CO.O), 76.213 (C-9).
114[6]	173.26/168.76 (C-8/1), 138.44/131.93/129.13/126.4 (C-19/29/28/20), 84.242 (C-32), 79.984/79.887/79.744 (C-10/26/9), 72.737 (C-2).
116	213.24 (C-22), 168.09/166.97 (C-1/8), 155.52 (O.CO.N), 137.69/131.32/130.45/123.89 (C-19/29/28/20), 8.891 (25-methyl).

1) 250 MHz/CD_3OD

2) 250 MHz/$CDCl_3$

3) 500 MHz/$CDCl_3$+CD_3OD

4) 330°K

5) 323°K

6) 320°K

7) 250 MHz

The compounds of the invention in free form or pharmaceutically acceptable salt form, hereinafter briefly named the **"agents of the invention"**, possess pharmacological activity. They are thus indicated for use as pharmaceuticals. In particular they possess antiinflammatory, and immunosuppr ssant and antiproliferativ activity.

The **antiinflammatory** activity may e.g. be determined in the following test methods, wherein abbreviations have the following significance:

DNP = 2,4-dinitrophenol
DNFB = 2,4-dinitrofluorobenzene
TPA = 12-O-tetradecanoylphorbol-13-acetate

1. Inhibition of mast cell degranulation in vitro

Murine mast cells (CFTL-12) are treated with DNP-specific IgE overnight. Degranulation is triggered by the addition of antigen (DNP) and measured as hexosaminidase activity in cell supernatant after 60 minutes in a colorimetric assay. Inhibitory substances are added 30 minutes prior to DNP.

The agents of the invention elicit in this test degranulation of mast cells (IC_{50}) at a dosage from about 1 ng/ml to about 50 ng/ml.

2. Oxazolone-induced allergic contact dermatitis (mouse)

[the test method is as described in F.M. Dietrich and R. Hess, Int. Arch. Allergy 38 (1970) 246-259]:

The agents of the invention elicit in this test an activity (inhibition of inflammatory swelling) of up to 58 % upon a single topical application as a 0.01 % solution. Hydrocortisone (1.2 %) is inactive under these conditions in this model and indomethazine (3.6 %) inhibits inflammation by only 22 %.

3. DNFB-induced allergic contact dermatitis (swine)

(the test method is as described in e.g. EP 315 978):

Two topical applications of a 0.13 % formulation of the agents of the invention result in inhibition of the inflammatory reaction by up to 44 %.

4. Inhibition of phorbol ester (TPA) - induced irritant contact dermatitis (mouse)

(the test method is as described in e.g. EP 315 978):

The agents of the invention elicit in this test upon single application of a 0.4-3.6 % formulation an inhibition of the inflammatory reaction by up to 40 %.

5. Inhibition of arachidonic acid - induced irritant contact dermatitis (mouse)

Female NMRI mice are treated topically on both the inner and outer sides of the right ear with 10 µl of DAE 244 (DMSO/acetone/ethanol=2/4/4) containing the test compound (usually 1.2 and 3.6 %). After 30 minutes the right ear is treated topically with 10 µl (both inside and out) of acetone containing 1 mg of arachidonic acid. After a further 90 minutes the mice are sacrificed and the ears cut off at the cartilage line and weighed. The difference in weight between left and right ears is calculated and the % inhibition taken relative to the group treated with arachidonic acid alone.

The agents of the invention elicit in this test upon single application of a 0.4-3.6 % formulation an inhibition of the inflammatory reaction by up to 30 %.

6. Inhibition of ionophore (A 23187) - induced irritant contact dermatitis (mouse)

Female NMRI mice are treated topically on the inside of the right ear with 15 µl of acetone/10 % DMSO containing 15 µg of A 23187 with or without the test compound (usually 0.4 % and 1.2 %). After 7.5 h the mice are sacrificed and the ears cut off at the cartilage line and weighed. The difference between the left and right ears is calculated for each mouse and the % inhibition is taken relative to the group having received A 23187 alone.

The agents of the invention elicit in this test upon single application of a 0.4-1.2 % formulation an inhibition of the inflammatory reaction by up to 72 %. Indomethazine used for comparison inhibited inflammation by 44 % at 1.2 % concentration.

Immunosuppressant and **antiproliferative** activity may e.g. be determined in the following test methods:

7. Proliferative response of lymphocytes to allogen stimulation in the mixed lymphocyte reaction (MLR) in vitro

[the test method is as described in e.g. T. Meo, "The MLR in the Mouse", Immunological Methods, L. Lefkovits and B. Pernis, Eds., Academic Press, N.Y. (1979) 227-239]:

The agents of the invention elicit in this test suppression of mixed lymphocytes (IC_{50}) at a dosage of from about 10 ng/ml to about 100 ng/ml.

8. Inhibition of the primary humoral immune response to sheep erythrocytes in vitro

[the test method is as described in R.I. Mishell and R.W. Dutton, Science 153 (1966) 1004-1006; R.I. Mishell and R.W. Dutton, J. Exp. Med. 126 (1967) 423-442]:

The agents of the invention are active in this test with an IC_{50} of from about 0.0024 µg/ml to about 0.32 µg/ml.

9. Inhibition of proliferation of human keratinocytes

(the test method is as described in e.g. EP 539326):

The agents of the invention are active in this test at concentrations of from about 3 µM/ml to about 10 µM/ml, resulting in an inhibition of from about 20 % to about 50 %.

10. Inhibition of phorbol ester (TPA) - induced epidermal hyperproliferation (mouse)

For induction of epidermal hyperproliferation TPA (0.005 %) is applied to the pinna surface on days 1 and 3. The test compound is applied to the same sites once daily on days 1, 2, 3 and 4. The vehicle is applied in the same way to TPA-treated control animals. Evaluation of antiproliferative activity of the test compound is performed on day 4, 6 hours after the last application, by immunohistological examination of the incidence of BrdU-staining keratinocytes (BrdU injected one hour before the animals are sacrificed labels cells at the S-phase) and by measurement of the epidermal area per section area in test and control animals.

The agents of the invention elicit in this test upon 4 applications of a 0.4 - 1.2 % formulation an inhibition of BrdU-labeling by 60-70 % and an inhibition of epidermal hyperplasia by 17-42 %.

The agent of Examples 71 (and 6d) and the agent of Example 93, particularly the agent of Example 71 (6d) are the preferred agents for the above indications. It has for example been determined that in the above test 6. these agents in the form of a 1.2 % preparation have better activity than a corresponding 1.2 % preparation of indomethazine. It is, therefore, indicated that for the above uses the compounds of Examples 71 (6d) and 93 may be administered to larger mammals, for example humans, by similar modes of administration at similar or lower dosages than conventionally employed with indomethazine.

The agents of the invention are therefore indicated as antiinflammatory agents and as immunosuppressant and antiproliferative agents for topical and systemic use in the prevention and treatment of inflammatory and hyperproliferative conditions and of conditions requiring immunosuppression, such as

a) treatment of inflammatory and hyperproliferative skin diseases, such as atopical dermatitis, contact dermatitis and further eczematous dermatoses, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne, psoriasis and cutaneous tumors;

b) prevention and treatment of allergic diseases such as extrinsic asthma, rhinitis, conjunctivitis, atopic eczema, urticaria/angioedema, food/drug allergy and anaphylaxis;

c) prevention and treatment of

- resistance in situations of organ or tissue transplantation, e.g. of heart, kidney, liver, bone marrow and skin,
- graft-versus-host disease, such as following bone marrow grafts,
- autoimmune diseases such as rheumatoid arthritis, systemic Lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, Myasthenia gravis, diabetes type I and uveitis,
- skin manifestations of immunologically-mediated disorders; and
- alopecia areata.

The agents may be administered systemically or topically. For the above indications the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, beneficial results are indicated to be obtained systemically at daily dosages of from about 1.0 mg/kg to about 10 mg/kg animal body weight. An indicated daily

dosage in the larger mammal is in the range of from about 10 mg to about 1000 mg, conveniently administered, for exampl , in divided doses up to four times a day or in retard form. For topical use beneficial results are obtained upon local administration at a concentration of from about 1 % to about 3 % of active substance sev ral times daily, e.g. 2 to 5 times daily.

The agents of the invention may be administered by any conventional route, in particular nterally, e.g. orally, e.g. in the form of tablets or capsules, or topically, e.g. in the form of lotions, gels, creams, sprays, and solutions such as ophtalmic or nasal solutions or aerosols for local treatment of skin and mucosal membranes, e.g. the eye, respiratory tract, vagina, oral and nasal cavity.

Pharmaceutical compositions e.g. for topical application comprising an agent of the invention in association with a least one pharmaceutically acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms contain, for example, from about 0.0025 mg to about 50 mg of active substance.

Topical administration is e.g. to the skin. A further form of topical administration is to the eye, e.g. for the treatment of immune-mediated conditions of the eye, such as: autoimmune diseases, e.g. uveitis, keratoplasy and chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions and corneal transplants, by the topical administration to the eye surface of an agent of the invention in a pharmaceutically acceptable ophthalmic vehicle.

The ophthalmic vehicle is such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, e.g. the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may be e.g. an ointment, a vegetable oil or an encapsulating material.

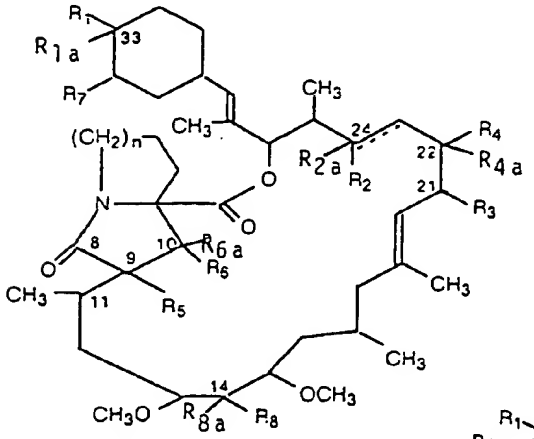
Whilst the antiinflammatory and immunosuppressant and antiproliferative activity is the main activity of the agents of the invention they also possess some degree of activity in increasing sensitivity to, or in increasing the efficacy of, chemotherapeutic drug therapy. This activity may e.g. be determined according to the test methods described in EP 360 760.

The compounds of the invention are therefore indicated for use in reversing chemotherapeutic drug resistance of varying types, e.g. acquired or innate, or in increasing sensitivity to administered drug therapy, e.g. as a means of reducing regular chemotherapeutic dosage levels, for example in the case of anti-neoplastic or cytostatic drug therapy, as a means of decreasing overall drug toxicity and, more especially, as a means of reversing or reducing resistance, including both inherent and acquired resistance, to chemotherapy.

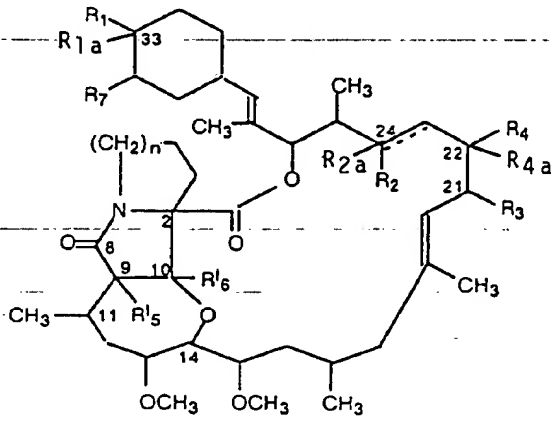
The invention thus also concerns the use of an agent of the invention as a pharmaceutical, particularly as an antiinflammatory, and as an immunosuppressant and antiproliferative agent; an agent of the invention for use as a pharmaceutical; the use of an agent of the invention for the preparation of a pharmaceutical composition which comprises mixing with at least one pharmaceutically acceptable carrier or diluent; and a process for the preparation of a pharmaceutical composition which comprises mixing an agent of the invention together with at least one pharmaceutically acceptable carrier or diluent. It further provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. It further provides a method of treatment of inflammatory and hyperproliferative conditions and of conditions requiring inmmunosuppression which comprises administering a therapeutically effective amount of an agent of the invention to a patient in need of such treatment.

Claims

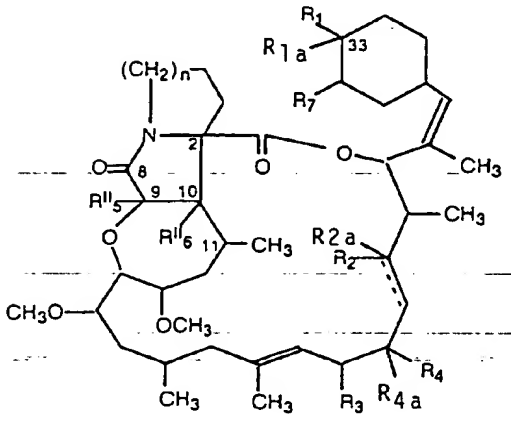
1. A compound of formulae I to III



I



II



III

wherein

the symbol ⎓ represents a single bond or, when R_{2a} is absent, a double bond;

R_1 represents an optionally protected hydroxy group and R_{1a} represents hydrogen; or R_1 and R_{1a} together represent oxo;

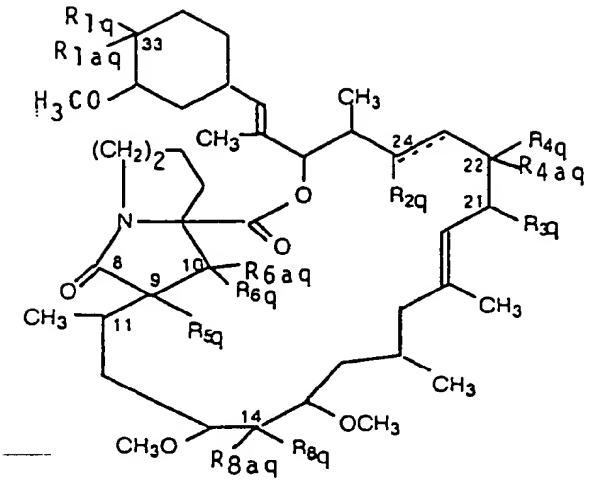
R_2 represents an optionally protected hydroxy group or together with R_4 forms the -OC(=O)O- group, and R_{2a} represents hydrogen or is absent;

whereby when the symbol ⎯⎯⎯ is a single bond;
R_2 together with R_{2a} also represents oxo;
R_3 represents methyl, ethyl, n-propyl or allyl;
R_4 represents optionally protected hydroxy or together with R_2 forms the -OC(=O)O- group, and R_{4a} represents hydrogen;
or R_4 together with R_{4a} represents oxo;
R_5 represents alkoxycarbonyloxy, halogen, optionally protected hydroxy, lower alkoxy, acyloxy or a group $-OC(=X)N(R_{10})R_{11}$;
or R_5 together with R_{6a} forms a group $-OC(=X)N(R'_{10})-$ attached with the nitrogen atom to the carbon atom carrying R_{6a}, whereby X represents oxygen or sulfur, R_{10} and R_{11} independently represent hydrogen or lower alkyl or together with the nitrogen atom form a five- or six-membered ring optionally containing a second heteroatom such as nitrogen or oxygen, and R'_{10} is hydrogen or lower alkyl;
or R_5 together with R_{6a} represents oxy, whereby R_6 represents hydroxy;
R_6 represents hydroxy, and R_{6a} represents hydrogen or together with R_5 forms a group $-OC(=X)N(R'_{10})-$ as defined above;
or R_6 and R_{6a} together represent oxo;
R'_5 represents optionally protected hydroxy, lower alkoxy or acyloxy and R'_6 represents hydroxy;
or R'_5 and R'_6 together form the -OC(=O)O- group;
R''_5 represents hydroxy or lower alkoxy and R''_6 represents hydroxy;
or R''_5 and R''_6 together form the -OC(=O)O- group;
R_7 represents methoxy or hydroxy;
R_8 represents an optionally protected hydroxy group, acyloxy, imidazolylcarbonyloxy or alkoxycarbonyloxy and R_{8a} represents hydrogen;
or R_8 represents hydroxy and R_{8a} together with R_5 represents oxy;
or R_8 together with R_{8a} represents oxo; and
n represents 1 or 2;
in free form or salt form.

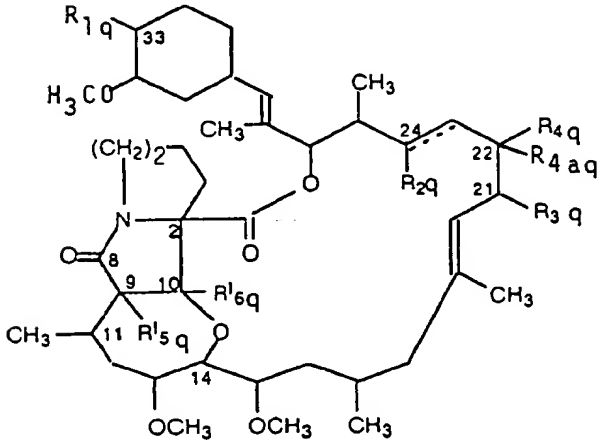
2. A compound according to claim 1 of formulae I to III as defined in claim 1, with the proviso that
R_2 and R_4 are other than together the -OC(=O)O- group;
R_4 is other than protected hydroxy;
R_5 is other than alkoxycarbonyloxy, halogen, protected hydroxy, a group $-OC(=X)N(R_{10})R_{11}$ as defined above or together with R_{6a} a group $-OC(=X)N(R'_{10})-$ as defined above;
R'_5 is other than protected hydroxy; and
R_8 is other than protected hydroxy or alkoxycarbonyloxy of altogether more than 2 carbon atoms,
in free form or salt form.

3. A compound according to claim 1 of formulae I to III as defined in claim 1, with the proviso that R_4, R_5 and R'_5 are other than protected hydroxy, and R_8 is other than alkoxycarbonyloxy of altogether more than 2 carbon atoms, in free form or salt form.

4. A compound according to claim 1 of formula Iq to IIIq

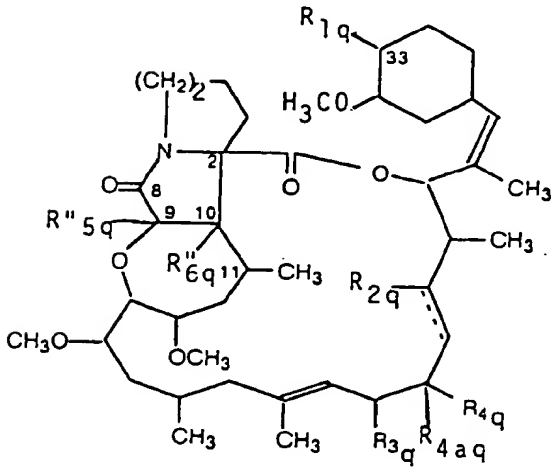


Iq



IIq

and



IIIq

wherein

R_{1q} represents hydroxy optionally protected by tert-butyldimethylsilyl or methylsulfonyl and R_{1aq} represents hydrogen;
or R_{1q} and R_{1aq} together represent oxo;

R_{2q} represents hydroxy optionally protected by tert-butyldimethylsilyl or together with R_{4q} forms the -OC(=O)O- group;

R_{3q} represents ethyl or allyl;

R_{4q} represents hydroxy optionally protected by tert-butyldimethylsilyl or together with R_{2q} forms the -OC(=O)O- group, and
R_{4aq} represents hydrogen;
or R_{4q} together with R_{4aq} represents oxo;

R_{5q} represents methoxycarbonyloxy; chlorine; hydroxy optionally protected by tert-butyldimethylsilyl, tert-butoxycarbonyl or methylsulfonyl; methoxy; formyloxy, acetoxy or benzoyloxy; or a group $-OC(=O)N(R_{10q})R_{11q}$ wherein R_{10q} and R_{11q} independently represent hydrogen or methyl or together with the nitrogen atom form 4-morpholinyl;
or R_{5q} together with R_{6aq} forms a group $-OC(=X)N(R'_{10q})-$ wherein X is as defined above and R'_{10q} is hydrogen or methyl;
or R_{5q} together with R_{8aq} represents oxy, whereby R_{8q} represents hydroxy;

R_{6q} represents hydroxy, and R_{6aq} represents hydrogen or together with R_{5q} forms a group $-OC(=X)N(R'_{10}q)-$ as defined above;
or R_{6q} and R_{6aq} together represent oxo;

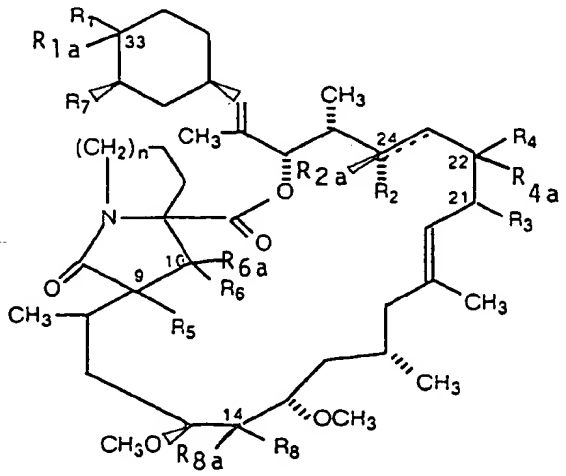
R'_{5q} represents hydroxy optionally protected by benzoyl or acetyl and R'_{8q} represents hydroxy;
or R'_{5q} and R'_{8q} together form the -OC(=O)O- group;

R''_{5q} represents hydroxy or methoxy and R''_{6q} represents hydroxy;
or R''_{5q} and R''_{6q} together form the -OC(=O)O- group; and

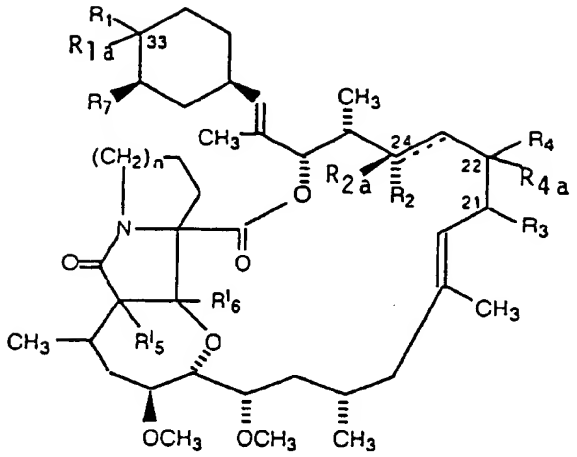
R_{8q} represents hydroxy optionally protected by tert-butyldimethylsilyl or methylsulfonyl; acetoxy or benzoyloxy; or 1-imidazolylcarbonyloxy; and R_{8aq} represents hydrogen;
or R_{8q} represents hydroxy and R_{8aq} together with R_{5q} represents oxy;
or R_{8q} together with R_{8aq} represent oxo;

in free form or salt form.

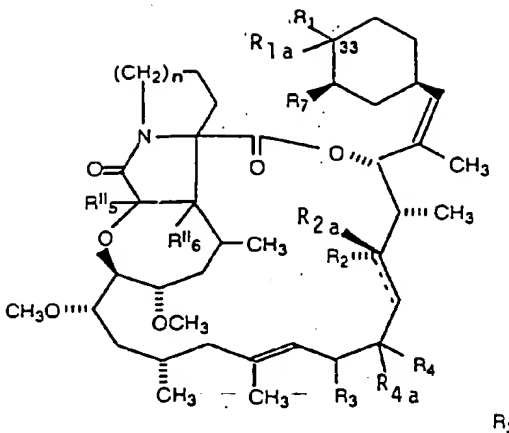
5. A compound according to claim 1 of formulae Is to Vs



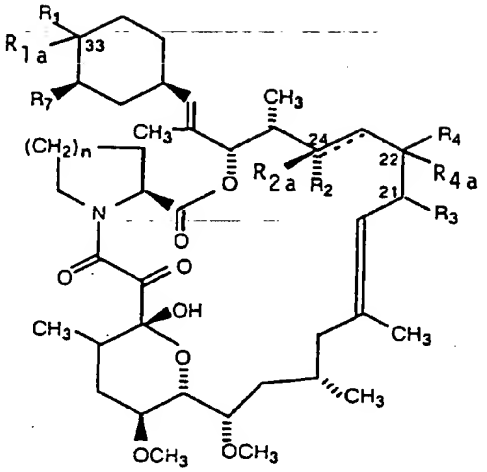
Is


R1
R1a
33
R7
CH3
CH3
24
R4
(CH2)n
O
R2a
R2
22
R4a
21
N
R3
O
O
R'6
CH3
CH3
R'5
O
OCH3
OCH3
CH3

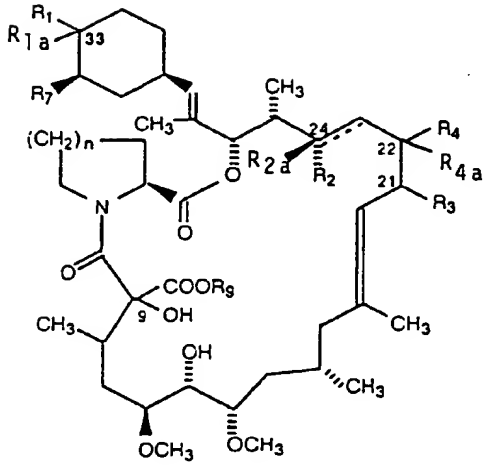
IIs



IIIs



IVs



Vs

wherein the substituents are as defined in claim 1,
in free form or salt form.

6. A compound according to claim 5 wherein
   - when R_1 is other than oxo together with R_{1a}, then R_1 preferably is bound with the α-configuration to the carbon atom in 33 position;
   - R_3 preferably is bound with the α-configuration to the carbon atom in 21 position;

- when R_4 is oth r than oxo together with R_{4a}, then R_4 preferably is bound with th α-configuration to the carbon atom in 22 position;

in fr form or salt form.

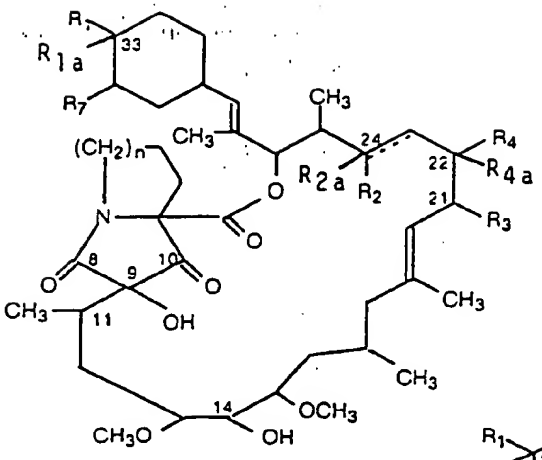
7. A compound according to claim 1 of formulae Iq to IIIq as defined in claim 4 having the stereochemical configuration indicated in claim 5 or 6 for the compounds of formulae Is to Vs, in free form or salt form.

8. The compound of formula I wherein
R_{1a}, R_{2a} and R_{8a} represent hydrogen;
R_1, R_2, R_5 and R_8 represent hydroxy;
R_3 represents ethyl;
R_4 and R_{4a} together, and R_6 and R_{6a} together, represent oxo;
the symbol ⎯⎯⎯ represents a single bond;
R_7 represents methoxy; and
n represents 2
(diastereoisomer B).

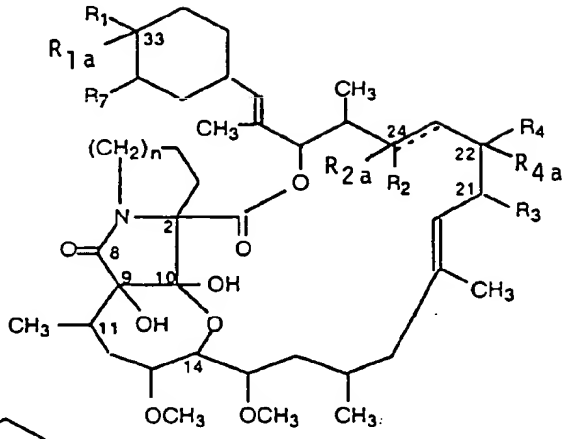
9. The compound of formula I wherein
R_{1a} and R_{2a} represent hydrogen;
R_1, R_2 and R_5 represent hydroxy;
R_3 represents ethyl;
R_4 and R_{4a} together, R_6 and R_{6a} together, and R_8 and R_{8a} together, represent oxo;
the symbol ⎯⎯⎯ represents a single bond;
R_7 represents methoxy; and
n represents 2
(diastereoisomer A).

10. The compound of formula I wherein
R_{1a} and R_{2a} represent hydrogen;
R_1 and R_2 represent hydroxy;
R_3 represents ethyl;
R_4 and R_{4a} together, and R_6 and R_{6a} together, represent oxo;
R_5 and R_{8a} together represent oxy;
R_8 represents hydroxy;
the symbol ⎯⎯⎯ represents a single bond;
R_7 represents methoxy; and
n represents 2
(diastereoisomer A).

11. A process for the preparation of a compound of formulae I to III as defined in claim 1, which comprises
a) for the production of a compound of formulae

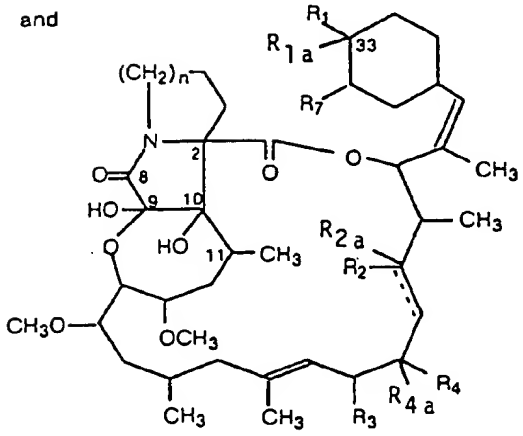


Ia



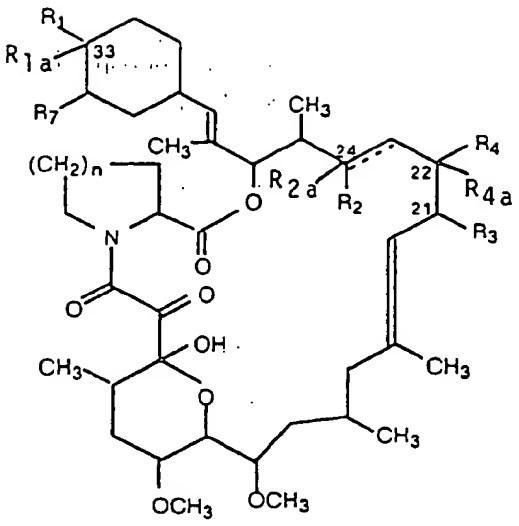
IIa

and



IIIa

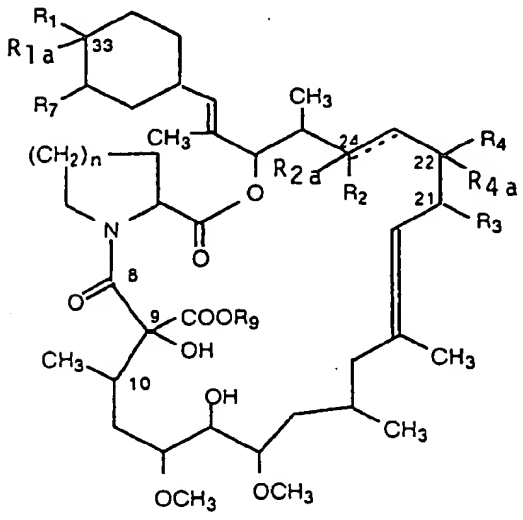
wherein the substituents are as defined in claim 1,
reacting a compound of formula IV



IV

wherein the substituents are as defined in claim 1, with an appropriate base or organic or anorganic salt, optionally in the presence of a phase transfer catalyst, or

b) for the production of a compound of formula Ia or IIa, reacting a compound of formula V



V

wherein R_9 represents alkyl and the other substituents are as defined in claim 1, with an appropriate base or organic or anorganic salt, optionally in the presence of a phase transfer catalyst, or

c) for the production of a compound of formulae I to III wherein R_2 and R_4, and/or R'_5 and R'_6 respectively R''_5 and R''_6 together form the -OC(=O)O-group, reacting a compound of formula I, II or III wherein R_2 and R_4, and/or R'_5 and R'_6 respectively R''_5 and R''_6 represent hydroxy, with phosgene, diphosgene or triphosgene in the presence of an acid binder, or

d) for the production of a compound of formulae I to III wherein at least one of the substituents R_1, R_2, R_4, R_6 or R_8 represents hydroxy, appropriately reducing a compound of formula I, II or III wherein at least one of the substituents R_1, R_2, R_4, R_6 or R_8 together with R_{1a}, R_{2a}, R_{6a} or, respectively, R_{8a} represents oxo, or

e) for the production of a compound of formulae I to III wherein R_5, R'_5 and R''_5 represent lower alkoxy, appropriately alkylating a compound of formula I, II or III wherein R_5, R'_5 and R''_5 represent hydroxy, or

f) for the production of a compound of formula I or II wherein at least one of the substituents R_6, R'_6 or

R_8 represents acyloxy, alkoxycarbonyloxy or -OC(=X)N(R_{10})R_{11}, appropriately acylating a compound f formula I or II wherein at least one of the substituents R_5, R'_5 or R_8 represents hydroxy, where indicated followed by the addition of NH_3 or of an appropriate amine, or

g) for the production of a compound of formula I wherein R_8 together with R_{8a} represents oxo, appropriately oxidizing a compound of formula I wherein R_8 represents hydroxy and R_{8a} represents hydrog n, or

h) for the production of a compound of formula I wherein R_5 represents halogen, appropriately halogenating a compound of formula I wherein R_5 represents hydroxy,

and/or optionally deprotecting a resultant compound of formulae I to III wherein a protected hydroxy group(s) is (are) present, and/or optionally protecting a resultant compound of formulae I to III wherein a free hydroxy group(s) is (are) present,
and recovering the resultant compound in free form or salt form.

12. A pharmaceutical composition comprising a compound of formulae I to III as defined in claim 1 in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent.

13. A compound of formulae I to III as defined in claim 1 in free form or in pharmaceutically acceptable salt form for use as a pharmaceutical.

14. A compound according to claim 13 for use as an antiinflammatory, or as an immunosuppressant and antiproliferative agent.

15. A process for the preparation of a pharmaceutical composition which comprises mixing a compound of formulae I to III as defined in claim 1 in free form or in pharmaceutically acceptable salt form together with at least one pharmaceutically acceptable carrier or diluent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 81 0325

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	EP-A-0 184 162 (FUJISAWA PHARMACEUTICAL CO., LTD.) * claims 1,2,15-18 *	1,5, 12-14	C07D491/18 C07D491/22 C07D498/18 C07D498/22
P,A	WO-A-9 213 862 (FUJISAWA PHARMACEUTICAL CO., LTD.) * claims 1,5-7 *	1,12-14	C07D498/04 C07H19/01 A61K31/33
P,X	* page 8, chemical formula *	5	A61K31/70 //(C07D491/18, 313:00,221:00, 209:00)
A	EP-A-0 480 623 (MERCK AND CO. INC.) * claims 1,6-9 *	1,12-14	
X	* page 3, chemical formula *	5	(C07D491/22, 321:00,313:00, 221:00,209:00)
A	EP-A-0 428 365 (MERCK AND CO. INC.) * claims 1,6-10 *	1,12-14	
X	* page 4, chemical formula *	5	(C07D491/22, 313:00,313:00, 221:00,209:00)
A	EP-A-0 413 532 (FISONS PLC) * claims 1,7,8 *	1,5, 12-14	(C07D491/22, 319:00,313:00, 221:00,209:00)
A	EP-A-0 402 931 (SANDOZ) * claims 1,7-9 *	1,5, 12-14	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D
C07H

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	16 AUGUST 1993	HASS C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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